D I B E N Z C Y C L O H E P T A D I E N E S

With Some Remarks on their Relationship to Degradation Products of Colchicine

A

T H E S I S

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C O N T E N T S

INTRODUCTION - FIRST SECTION

I

The present investigation was designed to elucidate some problems presented by the chemistry of colchicine, and the results are of interest primarily in view of their bearing on this field. For this reason it is necessary to survey the main features of the degradative chemistry of colchicine, to consider the molecular structure of the alkaloid, and to discuss, in some detail, the particular aspects which relate to the present inquiry.

II

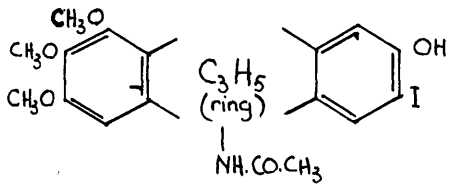
Colchicine is the toxic principle of the meadow saffron (Colchicum autumnale L.), and, on extracting the dried plant tissues with alcohol, a crude infusion of the alkaloid can be obtained. By a subsequent purification, which will be described in a later section (p.43), the crude extract furnishes the pure alkaloid in crystalline form.

Under mildly acidic conditions, colchicine is

hydrolysed to colchiceine.[2],[5] The latter, on treatment with iodine and caustic potash, undergoes degradation to N-Acetyliodocolchinol[8] - a reaction of fundamental importance in colchicine chemistry, in that it appears to effect a simplification and stabilisation of structure in the product. Consequently the whole field may be considered in two phases: firstly the conversion of colchicine to N-Acetyliodocolchinol, and secondly the further degradation of the latter to synthetic products of known configuration. It is convenient to examine the second phase before the first, and to establish, at the outset, the probable structure for N-Acetyliodocolchinol. Thereafter the behaviour of compounds having the same basic structure as colchiceine will be discussed, and an endeavour made to account for the transformation to N-Acetyliodocolchinol.

III

N-Acetyliodocolchinol has the properties of a true phenol.[8] Oxidation of the phenol itself to 3:4:5: trimethoxyphthalic acid, and of the phenol methyl ether to 4: methoxy-5: iodophthalic acid[9] [40] indicates the presence, in N-acetyliodocolchinol, of two different benzene nuclei, namely a vicinal trimethoxybenzene ring and a 4: hydroxy-5: iodobenzene ring. Moreover, as will appear later, the compound is an acetylated primary amine. The partial formula - $C_{15}H_8.(O.CH_3)_3.(OH).I.(NH.CO.CH_3)$ - indicates that the corresponding unsubstituted hydrocarbon ($C_{15}H_{14}$) is eighteen hydrogen atoms short of the paraffin ($C_{15}H_{32}$). Since sixteen of these are accounted for by the presence of two benzene rings, the absence of the other two hydrogen atoms requires the presence of a third ring. Now the tricyclic structure must have, as terminal rings, the two benzene nuclei which, after oxidation, appear as substituted phthalic acids: whilst the acetylamino group, being absent from these nuclei, must reside in the middle ring. These considerations are summarised in the partial formula I.



I

The methyl ether of N-acetyliodocolchinol provides, on reductive de-iodination, N-acetylcolchinol methyl ether, which yields in turn the free base, colchinol methyl ether, on acidic hydrolysis.(8) The amino-group in this base (and, by inference, the acetylamino-group in N-acetyliodocolchinol) is shown to be a primary amine by exhaustive methylation; and decomposition of the quaternary ammonium hydroxide leads to a methoxylated hydrocarbon,(10) deaminocolchinol methyl ether.§§

In order to determine the carbon skeleton of this important degradation product, Windaus treated deaminocolchinol methyl ether with hydriodic acid, so as to demethylate the four methoxyl groups, and then subjected the crude demethylated material to distillation from zinc dust. He obtained from the distillate a very small amount of a hydrocarbon which was identical with 9-methylphenanthrene.(10)

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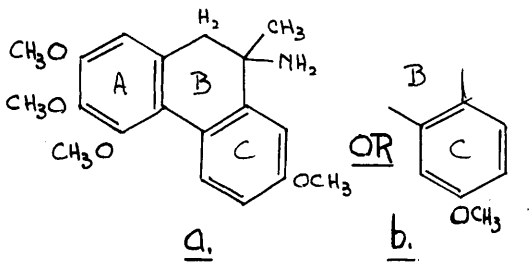
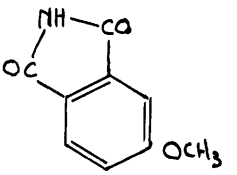
§§ Cook and Graham(13) subsequently discovered that the deamination could be more expeditiously effected by heating N-acetylcolchinol methyl ether with phosphorus pentoxide in xylene - an unusual method of deamination to which reference is made later.

On that account Windaus concluded that deaminocolchinol methyl ether was a tetramethoxy-9-methylphenanthrene, and that the parent amine, colchinol methyl ether was a tetramethoxy-9:(or 10)amino-9:methyl-9:10:dihydro-phenanthrene.



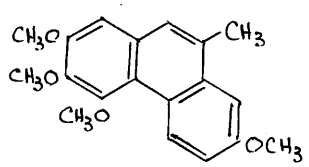
II



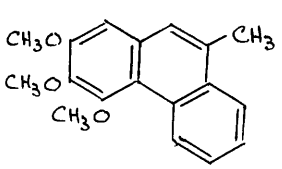
III

Several alternative formulae conform to this general type, but Windaus was led to prefer one or other of the formulae IIa or b for colchinol methyl ether. In the first place, preferential demethylation of the methoxy-groups in the (trimethoxy) ring A, which accompanies the hydrolytic removal of the acetyl group from N-acetylcolchinol methyl ether, renders that ring more susceptible to oxidation, and 4:methoxyphthalimide (III) can be isolated from the chromic acid oxidation products of this partially demethylated material.(9) This favours the suggestion that the amino-group is only one carbon-atom removed from the (monomethoxy) ring C,

as in IIa and b. Secondly, Windaus assumed that colchinol methyl ether would possess a free methylene group, since colchicine itself appears to possess such a group which can be oxidised to a carbonyl group.[4],[10] On this assumption the methyl and amino groups must both occupy the same 9-position (as in IIa and b). Thirdly, the orientation of ring A, with respect to the rest of the molecule in degradation products of colchicine, was deduced by Windaus as a result of an oxidative degradation§§, whose ingenious interpretation led him to assign, to this group of compounds, a 2:3:4-trimethoxy-configuration (as in IIa and b), rather than the alternative 1:2:3-trimethoxy structure. The corresponding formula for deaminocolchinol methyl ether is, therefore, IVa or IVb - the position of the methoxyl group in ring C being uncertain.



IV(a)



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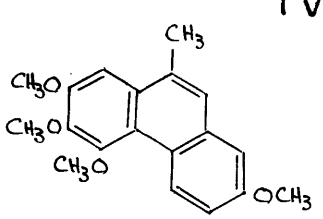
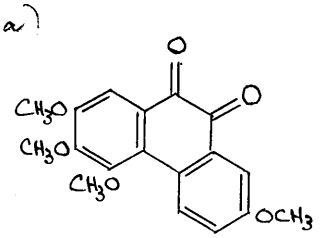
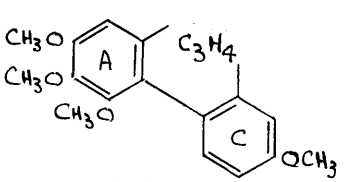


V



VI



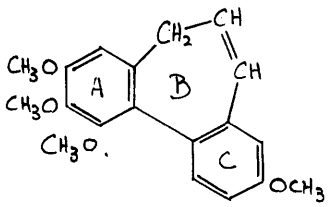
VII

§§ This interesting series of reactions (7) which is here omitted in the interest of brevity, has been concisely summarised by Windaus (Ref.10, pp 67-69)

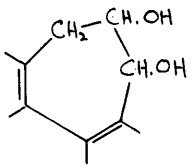
When, however, the required tetramethoxy-9:methylphenanthrenes IVa and IVb were synthesised by Buchanan, Cook, and Loudon[14] and were compared with deaminocolchinol methyl ether, it was found that the latter was distinct from each of the former (IVa and b). Moreover, in its ease of hydrogenation and in its failure to form a picrate, deaminocolchinol methyl ether differed so markedly from the behaviour of its two isomers (IVa and IVb) that formulation as a methoxymethylphenanthrene (such as V) was altogether excluded.[15] On the other hand, Barton, Cook, and Loudon[15] demonstrated that deaminocolchinol methyl ether yielded, on chromic acid oxidation, two products: one having the properties of an α:ß: unsaturated ketone, and the second being 2:3:4:7:tetramethoxyphenanthraquinone (VI), identical with a synthetic specimen. The appearance of this quinone on oxidation finally settled the methoxylation pattern (VII) of the two flanking rings, but left the nature of the middle ring to be determined.

This problem was then solved by the same authors[15] through the use of a stepwise oxidation of an olefinic double-bond, whose presence was suggested by the ready hydrogenation over palladium. Oxidation of the double-bond in deaminocolchinol methyl ether with osmium tetroxide,

followed by scission with lead tetra-acetate, gave rise to a mono-aldehyde containing the same number of carbon atoms as the original olefin. Now scission of an exocyclic double bond would have resulted in removal of a carbon fragment, so that the double bond must have resided <u>in</u> the ring - a conclusion which can be accomodated only in a seven-membered ring formulation.



VIII



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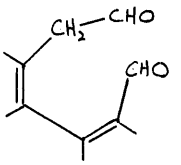

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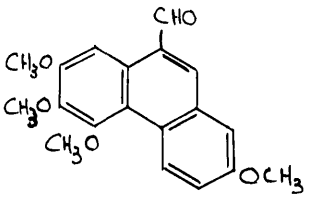

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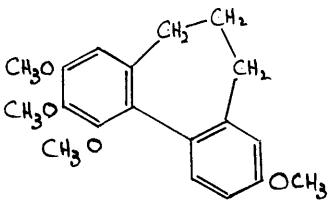

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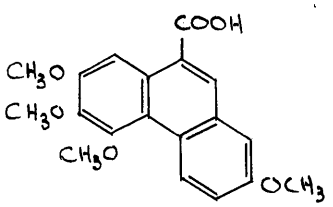

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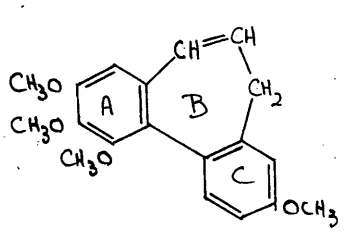
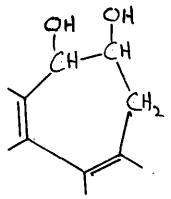


XIV



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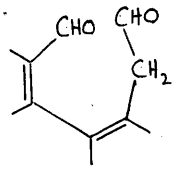
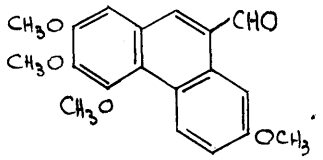


XVI



XVII

Two formulae of this type (VIII and XIV) are permissable, and the oxidative scission will be represented by formulae VIII to XI, or else by XIV to XVII. Oxidation of the mono-aldehyde to the known acid XIII demonstrated that the aldehyde was, in fact, XI. Consequently deaminocolchinol methyl ether must be regarded as 9:12:13:14:tetramethoxy-3:4:5:6:dibenzcyclohepta-1:3:5:triene VIII[§§].

Confirmatory evidence for this formulation was adduced by Barton, Cook, and Loudon[15] in the behaviour of iso-deaminocolchinol methyl ether, formed in small amount along with VIII when N-acetylcolchinol methyl ether is deaminated by the procedure of Cook and Graham.[13] This isomer has the same dihydride (XII) as deaminocolchinol methyl ether, and must have the structure XIV. And, in fact, iso-deaminocolchinol methyl ether was converted to the expected synthetic aldehyde, XVII by means of an exactly analogous oxidation.

In apparent conflict with a dibenzcycloheptatriene structure for deaminocolchinol methyl ether are the degradation to 9-methylphenanthrene on treatment with hydrogen iodide followed by distillation from zinc

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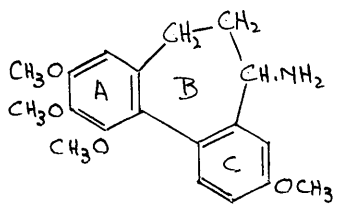
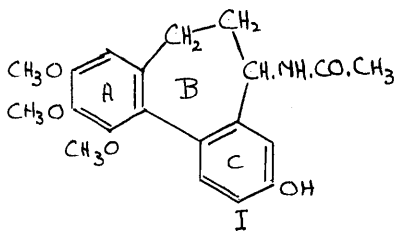
§§ The system of numbering is described in a footnote on page 14 .

(p.4), and the oxidation to tetramethoxyphenanthraquinone with chromic acid (p.7),. Reference will be made to these discrepancies in a later section.

Making the probable assumption that the Hoffmann deamination involves no change in the carbon skeleton;§§ the parent amine colchinol methyl ether may be regarded as an aminodibenzcycloheptadiene. The location of the amino-group is uncertain, but Windaus' oxidation to 4-methoxyphthalimide (p.5), slightly favours the 2-position (as shown in XVIII). On this basis the structure of N-acetyliodocolchinol will be XIX. The same middle ring may also be present in colchicine itself, although definite proof is lacking.



XVIII



I

XIX

To summarise: Ring A in N-acetyliodocolchinol and its degradation products is a 2:3:4-trimethoxybenzene ring. Ring B is known to be seven-membered in the case of deaminocolchinol methyl ether and may be present in the

§§ Compare Ref. 16

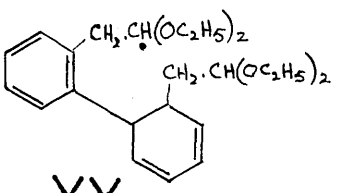
immediate precursors of the latter. The position of the amino-(or acetylamino-)group in these precursors is not determined, though it may be attached to the carbon-atom " α - " to ring C. In the same series of degradation products, ring C is a hydroxylated (or methoxylated) benzene ring of unambiguous orientation.

PART I 3:4:5:6-DIBENZCYCLOHEPTA-1:3:5-TRIENE

In view of the fundamental importance of any structure assigned to deaminocolchinol methyl ether - bearing, as it does, on the wider problem of the structure of colchicine - it was of importance to obtain confirmatory evidence for its formulation as a methoxylated dibenzcycloheptatriene (VIII). Accordingly, pending a successful synthesis of the proposed structure, an investigation of simpler substances possessing the same ring structure was undertaken. Our attention was more especially directed towards finding out whether 3:4:5:6-dibenzcyclohepta-1:3:5-trienes of known structure would undergo those anomalous reactions already noted in the case of deaminocolchinol methyl ether (compare pp.9/10) which are apparently incompatable with formulation of the latter as a compound of this type.

Few compounds having this arrangement of carbon atoms are recorded in the literature, and their chemistry has not been investigated in detail. Weitzenböck[17] prepared the aldehydodibenzcycloheptatriene XXI by self-condensation of the bisacetal of

diphenyl-2:2'-diacetaldehyde (XX), and the heptatriene was found to undergo oxidation to phenanthraquinone on oxidation with chromic acid. This oxidative contraction to a six-membered ring is notable as a reaction of an authentic dibenzcycloheptatriene which affords a parallel to the oxidation of deaminocolchinol methyl ether (p.7). Borsche and Herbert[18] describe a condensation of 2-bromo-5-nitroacetophenone (XXII) to the methylcycloheptatrienone (XXIV) by heating with copper. It is probable that in this case the 2:2'-diacetyl-dinitrodiphenyl (XXIII) is formed intermediately by a reaction of the Ullmann type.



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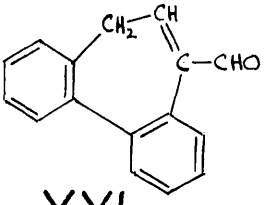
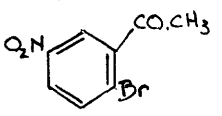


XXI



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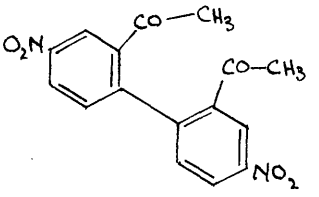
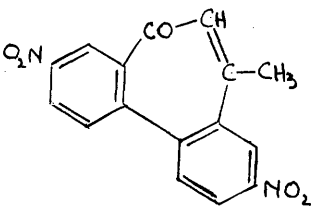


XXIII



XXIV

The most extensive investigation, however, was carried out by Kenner and Turner,[19] and by Kenner[20]

who prepared a series of 1- and 2- substituted dibenzcycloheptadienes,§§ utilising 2:2'-dibromomethyldiphenyl (XXV) as starting material. Seven-membered ring formation in the case of such o-o'-disubstituted diphenyls appears to occur with great ease - indeed Kenner compares it to the ease of formation of the indane ring from o-xylylene dibromide - and this is exemplified in that the dinitrile XXVI readily undergoes an internal Thorpe reaction to give XXVII; and again XXV can be brought to react with only one molecule of malonic ester to furnish the ester XXIX in excellent yield.

These materials were utilised by Kenner to prepare 1-Amino-dibenzcycloheptadiene (XXXII) by two methods. In the first of these, the cyano-imide (XXVII) was hydrolysed in two stages to the ketone XXVIII whose oxime yielded the amine XXXII on reduction with sodium in alcohol.

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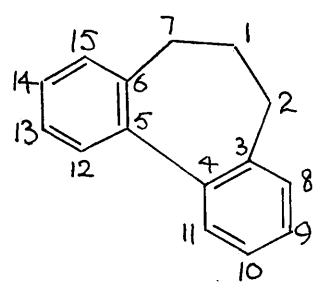
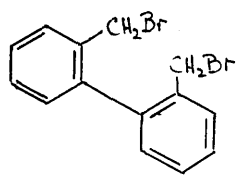
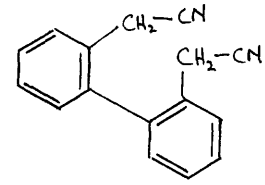
§§



The system of numbering adopted is that advocated by Kenner and Turner (19).



XXV



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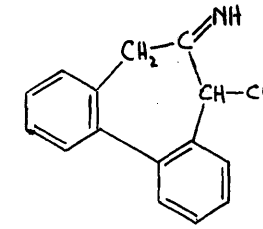
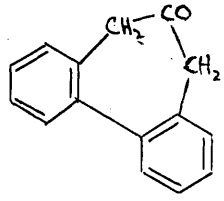
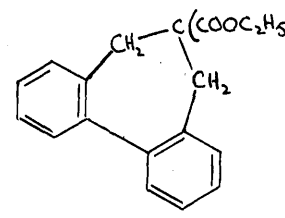


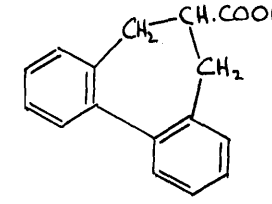
XXVII



XXVIII



XXIX



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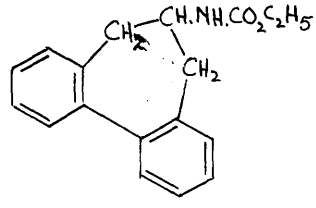
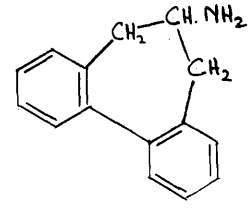
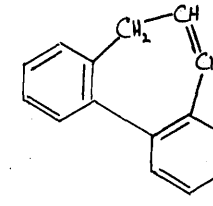


XXXI



XXXII



XXXIII

In the second method, the ester XXIX was converted by hydrolysis and loss of carbon dioxide to the acid XXX which was then degraded by the Curtius technique to the urethane XXXI. Hydrolysis of XXXI then gave the amine XXXII.

Deamination of XXXII would lead to 3:4:5:6-dibenz-cyclohepta-1:3:5-triene XXXIII, and Kenner affirmed his

intention of preparing the triene and comparing its properties with those of indene which he expected it to resemble, in view of the general similarity between the properties of o-disubstituted benzenes and those of o-o'-disubstituted diphenyls. This proposed investigation was not carried into effect. By a thermal decomposition of the hydrochloride of XXXII, however, Kenner obtained a picrate which he described as dibenzcycloheptatriene picrate on the basis of its analytical composition.

Since this investigation manifestly provided a route already prospected to our desired destination, a repetition of Kenner's work was carried out. Hydrolysis of the urethane XXXI gave a base differing appreciably, in the melting points of its hydrochloride and its acetyl derivative from Kenner's recorded results (compare Experimental). The same material was, however, obtained on repeating Kenner's first synthetic route, namely by reduction of the oxime of XXVIII, and moreover, analysis of the compounds leads to the expected results. Accordingly the identity of the amine is not in doubt. In the experimental part are recorded some amendments to Kenner's procedure:

bromination of o:o'-ditolyl is effected in considerably enhanced yield by a modified technique; hydrolysis of the urethane XXXI with alcoholic alkali conveniently replaces the more cumbersome treatment with hydrochloric acid in a sealed tube; and reduction of the oxime of XXVIII is carried out catalytically with Raney nickel under pressure using the method of Paul.[21] Attempts to modify the Curtius degradation of the acid XXX, by employing the methods of Schmidt[22] or of Nelles,[23] were ineffectual.

Deamination of the base is most conveniently effected by treatment of the corresponding N-acetyl derivative with phosphorus pentoxide in boiling xylene - a reaction first encountered by Cook and Graham[13] in the case of colchinol methyl ether[§§] - whereby an oily unsaturated hydrocarbon is obtained, whose analytical composition and hydrogen absorption over palladium black require its formulation as 3:4:5:6-dibenzcyclo-hepta-1:3:5-triene XXXIII, and this is confirmed by its ready conversion to a crystalline dibromide (XXXIV) on treatment with bromine in acetic acid. The same triene is produced on similar phosphoric oxide treatment of the corresponding urethane XXXI, although the deamination

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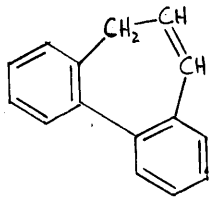
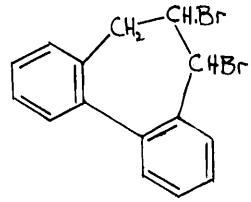
§§ This reaction is discussed more fully in an Appendix.

proceeds less readily in this case and an unidentified by-product is formed simultaneously.



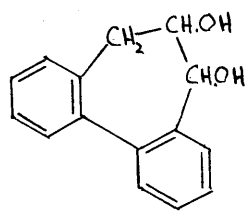
XXXIII



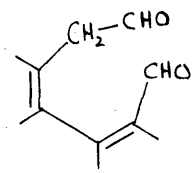
XXXIV

In view of Kenner's claim[20] to have isolated the picrate of 3:4:5:6-dibenzcyclohepta-1:3:5-triene, it was somewhat surprising to find that the new hydrocarbon showed no evidence of picrate formation in ethanol - being, indeed, similar in this respect to deaminocolchinol methyl ether, from which, likewise, no picrate could be obtained. It was clearly desirable to obtain the picrate which Kenner had obtained from the oily residue remaining after thermal decomposition of the hydrochloride of XXXII. Accordingly the hydrochloride was decomposed by heating to yield an oil, separated by distillation into solid and liquid fractions. The liquid was shown to contain the triene by comparison of the dibromide with the dibromide XXXIV, whilst the solid was identified as 9-methylphenanthrene by direct comparison, and by formation of the picrate.

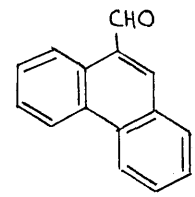
No other picrate-forming hydrocarbon has been encountered. The analytical composition of Kenner's picrate would, of course, agree equally well with that of the isomeric 9-methylphenanthrene picrate§§, but it can scarcely have been the latter compound. Not only is its melting-point (137°) different from that of the latter (153°- 154°), but it was found by Kenner to depress the melting-point (147°- 149°) of a second picrate which he obtained from the products of thermal decomposition of the barium salt of dibenzcycloheptadiene-1-carboxylic acid (XXX). It is probable that this second picrate was 9-methylphenanthrene picrate, since repetition of the thermal decomposition of the barium salt (see Experimental) furnished some 9-methyl-phenanthrene. At Professor Cook's request, Professor Kenner kindly undertook a search for his original sample of the picrate, but it was, unfortunately, no longer in his possession.



XXXV

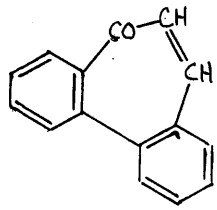


XXXVI

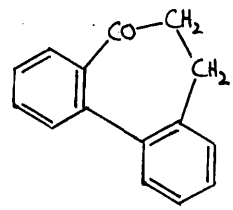


XXXVII

§§ 9-Methylphenanthrene was unknown when Kenner carried out his investigation. It was first synthesised by Windaus, Jensen, and Schramme in 1923.(12).



XXXVIII



XXXIX

The behaviour of 3:4:5:6-dibenzcyclohepta-1:3:5-triene during oxidation was now investigated. With osmium tetroxide, hydroxylation of the olefinic 1:2-double bond took plane, forming 3:4:5:6-dibenzcyclohepta-3:5-diene-1:2-diol XXXV. On scission of the latter by means of lead tetra-acetate, an uncrystallisable gum was obtained which, however, after warming with sodium carbonate in ethanol, deposited crystals of phenanthrene-9-aldehyde (XXXVII) identified by oxidation to the 9-carboxylic acid (see Experimental). Presumably the expected di-aldehyde XXXVI, initially produced in the reaction, undergoes self-condensation under these mildly alkaline conditions. This series of reactions - hydroxylation, scission, self-condensation - is an exact replica of the behaviour of deaminocolchinol methyl ether and of its isomer, iso-deaminocolchinol methyl ether (p.9).

With sodium dichromate in acetic acid, the triene

yielded a mixture of products separated by alkaline extraction and chromatography into phenanthrene-9-carboxylic acid (identified by mixed melting-point), phenanthraquinone (identified by phenazine formation and mixed melting-points), and a ketonic by-product. The formation of phenanthrene-9-carboxylic acid implies an oxidative scission of the double bond, followed by re-condensation - possibly by the same mechanism as that outlined above - and further oxidation of this carboxylic acid[24] would explain the appearance of phenanthraquinone. The ketonic by-product had the properties of an α:ß: unsaturated ketone, and its formulation as 3:4:5:6-dibenzcyclohepta-1:3:5-triene-7:one (XXXVIII) is supported by its uptake of one molecule of hydrogen to yield the saturated 3:4:5:6-dibenzcyclohepta-3:5-diene-2:one (XXXIX). A similar oxidation of the reactive 7-methylene group in XXXIII (activated by the benzene ring and by the double-bond) takes place during selenium dioxide oxidation, when an improved yield of the same ketone XXXVIII was obtained. It will be recalled that deaminocolchinol methyl ether is oxidised to an unsaturated ketone and a phenanthraquinone, when oxidised with sodium dichromate (p.7).

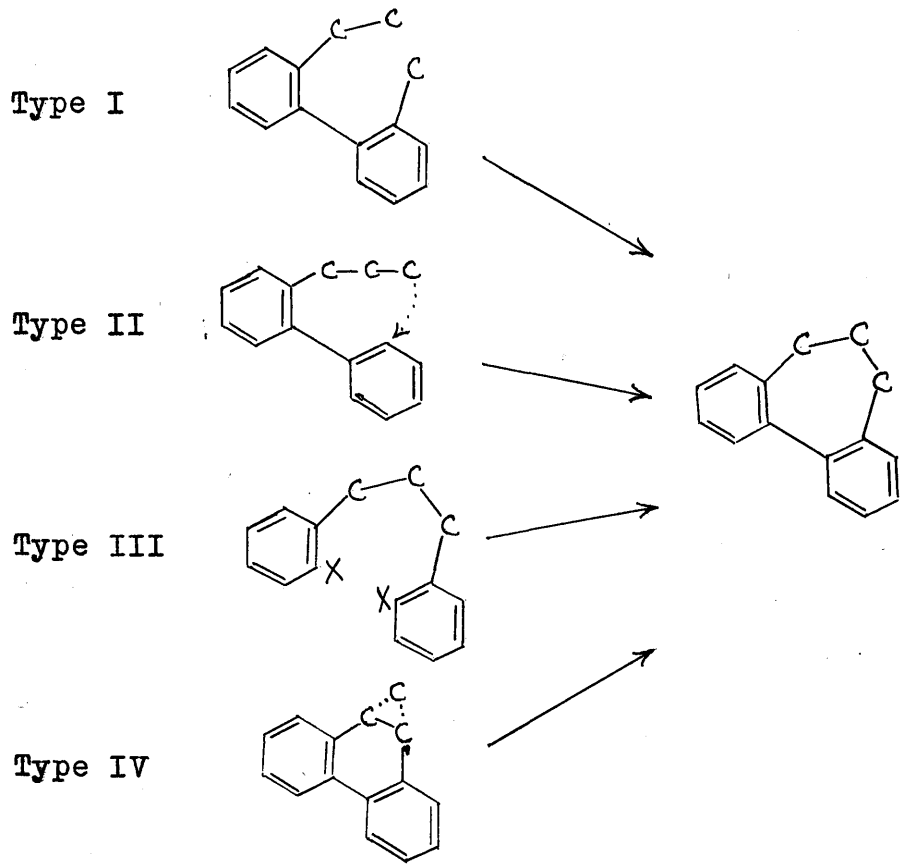
On account of Windaus' degradation of deaminocolchinol methyl ether to 9-methylphenanthrene, it was particularly desirable to reconcile this reaction with the proposed methoxydibenzcycloheptatriene structure VIII proposed for deaminocolchinol methyl ether by ascertaining whether 3:4:5:6-dibenzcyclohepta-1:3:5--triene itself could be made to isomerise to 9-methylphenanthrene. The production of the latter on decarboxylation of dibenzcycloheptadiene-1-carboxylic acid (XXX), and its presence along with dibenzcycloheptatriene amongst the thermal decomposition products of the hydrochloride of 1-aminodibenzcycloheptadiene (XXXII) suggested that isomerisation of the triene might, indeed, be fairly readily accomplished: but, in the event, this expectation was not fulfilled. Apart from some resinification, the triene was recovered unchanged after prolonged heating either alone or over sodium ethoxide; and distillation under reduced pressure from anhydrous zinc chloride afforded a small amount of high-boiling, unsaturated oils - presumably polymerides. On the other hand, when subjected to those conditions used by Windaus to demethoxylate

deaminocolchinol methyl ether - namely successive treatment with hydrogen iodide and distillation from zinc dust - the triene gave, at the first stage, a saturated iodo-compound which, with zinc dust (or better with sodium ethoxide) was subsequently de-iodinated to 9-methylphenanthrene. Lack of material prevented further inquiry to determine at which stage (iodination or de-iodination) the rearrangement had occurred.

Accordingly it is concluded that 3:4:5:6-dibenz-cyclohepta-1:3:5-triene in its failure to form a picrate, in its oxidation and reduction, and in its isomerisation to 9-methylphenanthrene closely resembles the behaviour of deaminocolchinol methyl ether; and thus lends support to the conclusion that the latter is a tetramethoxydibenzcycloheptatriene.

PART II THE RING-CLOSURE OF ß-(DIPHENYL-2)-PROPIONIC ACID

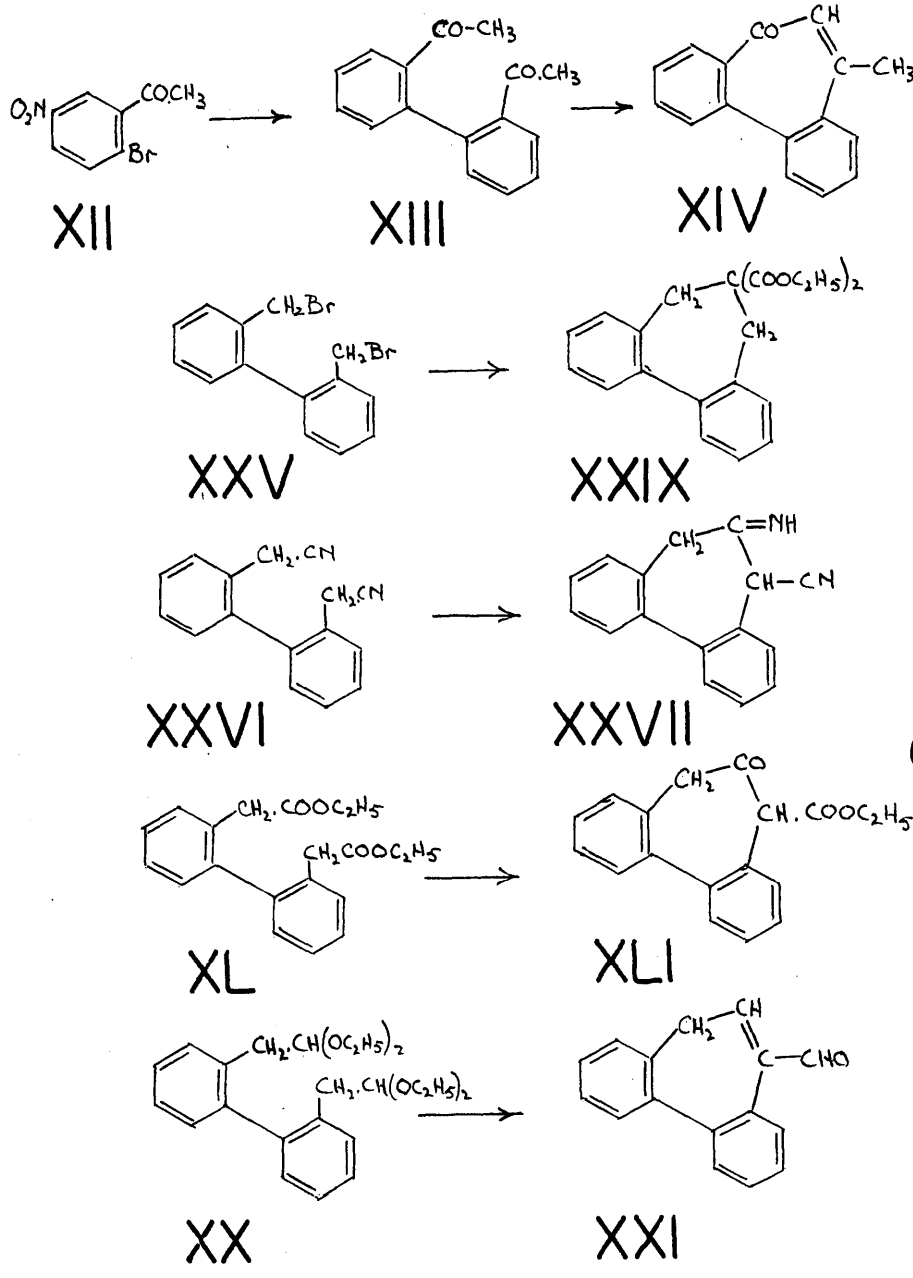
The 3:4:5:6-dibenzcycloheptadiene ring system, being in effect a diphenyl molecule "bridged" across two o:o'-positions by a three-carbon chain, is theoretically capable of construction in four ways.



In the first place two side-chains already attached to the two o:o'-diphenyl positions (and

carrying suitable reacting groups) may be joined to form the "bridge" : alternatively the terminal group of a three-carbon chain, attached to an o-position in the diphenyl molecule, may be induced to substitute in a free o′-position in the other benzene ring and in this way bridge the two o- and o′ positions: or, thirdly, the phenyl nuclei of a 1:3-diphenylpropane molecule may be united by a diphenyl bond, using an intra-molecular reaction of the Ullmann or of the Pschorr type. Finally, the seven-membered ring might be derived from a six-membered phenanthrene system by a process of ring enlargement.

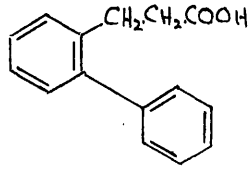
Examination of the recorded syntheses of 3:4:5:6--dibenzcycloheptadienes and -trienes (to which reference has already been made: pp.13,14) indicates that, with one exception, the ring closure stages are of the first general type, utilising o-o′-diphenyl derivatives as precursors; and, even in the exceptional case of the reaction (XXII → XXIV) described by Borsche and Herbert,[18] an analogous o-o′-diacetyldiphenyl (XXIII) is probably formed intermediately, since the reaction is carried out by heating the reagent XXII with copper bronze.



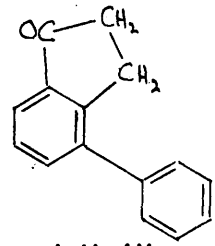
(20)

An assessment of the practicability of the second general synthetic route was desirable, more particularly

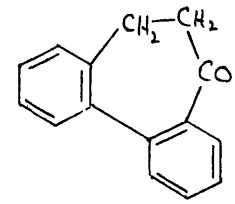
because unsymmetrically substituted ß -(diphenyl-2)--propionic acids are more accessible than unsymmetrically substituted 2:2'ditolyls. The ring-closure of ß -(diphenyl-2)-propionic acid itself (XLII) may give rise to two compounds depending on whether the substitution occurs in the same ring as the propionic acid residue, giving 4-phenylhydrindone (XLIII), or in the other ring, giving 3:4:5:6-dibenzcycloheptadiene--2-one (XXXIX). Von Braun and Manz,[25] who had already investigated this ring-closure, concluded that only the former compound (XLIII) was obtained, but their published experimental evidence - in respect of both the characterisation and the alleged homogeneity of their product - seemed inadequate to support their findings. They obtained an oily ketone, purified by distillation and oxidised to an acid which they believed to be a benzene-1:2-dicarboxylic acid because it gave a qualitative fluorescein reaction with resorcinol. On this account, they deduced that the ketonic product was XLIII and assumed that it was homogeneous since it gave a sharp-melting semicarbazone, for which, however, no analytical figures were published.



XLII



XLIII

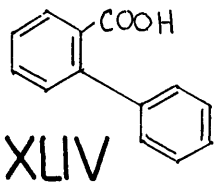


XXXIX

As a preliminary to an investigation of this ring-closure, a suitable means was sought to identify small quantities of the dibenzcycloheptadienone XXXIX already available, in small amount, through the hydrogenation of the unsaturated ketons XXXVIII (see p.21). In a model experiment, the more plentiful 3:4:5:6-dibenzcycloheptadiene-1-one (XXVIII) was found to be oxidised, with sodium dichromate in acetic acid, to phenanthraquinone and diphenic acid, and the same products were then found to result from similar oxidation of dibenzcycloheptadiene-2-one (XXXIX). Since phenanthraquinones are readily separable (if necessary by chromatography) from other neutral oxidation products, this reaction affords an elegant test for the presence of 3:4:5:6--dibenzcycloheptadiene-ones in ketone mixtures; and indeed dichromate oxidation to phenanthraquinones has subsequently been used by others in these laboratories as a test diagnostic of the 3:4:5:6-dibenzcycloheptadienone system. An attempt to oxidise with selenium

dioxide the reactive methylene groups in Kenner's dibenzcycloheptadiene-1-one (XXVIII), led to phenanthraquinone as the only isolable product.

The synthesis of ß-(diphenyl-2)-propionic acid was now undertaken by the following route;-



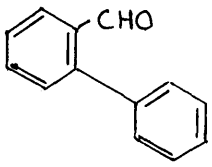
XLIV

$R\,CO.NH.NH_2$

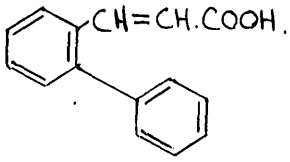
XLV

$R.CO.NH.NH.SO_2Ph.$

XLVI



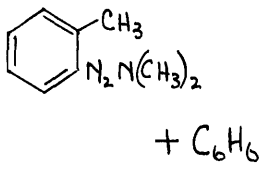
XLVII



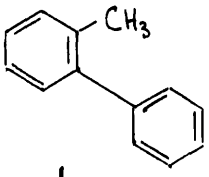
XLVIII

Diphenyl-2-carboxylic acid (XLIV) was converted via its methyl ester, hydrazide (XLV) and benzenesulphonhydrazide (XLVI) to diphenyl-2-aldehyde (XLVII) according to the procedure of McFadyen and Stevens,[26] and the aldehyde was then condensed with malonic acid to yield ß-(diphenyl-2)-acrylic acid (XLVIII) which was hydrogenated to ß-(diphenyl-2)-propionic acid (XLII). An unexpected discrepancy in the melting-point and water solubility of this acid, compared with the

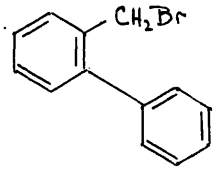
properties recorded by von Braun and Manz, led us to repeat the later stages of their synthesis. They had prepared their acid from the diethyl ester LII produced by condensation of 2-bromomethyldiphenyl (LI) with malonic ester. Accordingly, bromomethyldiphenyl was prepared conveniently, but in low overall yield, by the following new route:-



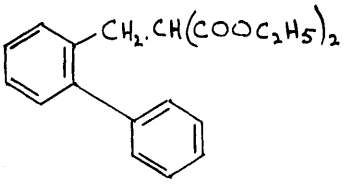
XLIX



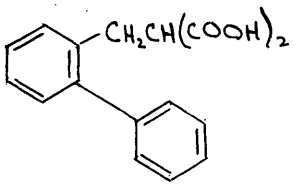
L



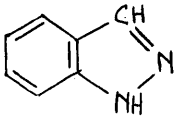
LI



LII



LIII



LIV

o-Tolyltriazen (XLIX), prepared by the method of Elks and Hey,[27] was condensed with benzene in the presence of glacial acetic acid to give 2-methyldiphenyl (L) in low yield, most of the triazen being converted

to benzpyrazole (LIV)§§. Bromination of the methyl group gave 2-bromomethyldiphenyl (LI) which condensed with malonic ester to provide the di-ester LII. The properties of the bromomethyl compound and of the di-ester agreed with those recorded by von Braun and Manz, and moreover the di-ester LII on hydrolysis yielded an acid whose properties (melting-point and solubility) corresponded to those which the same authors attributed to ß-(diphenyl-2)-propionic acid. This acid, however, was shown by analysis to be o-phenylbenzylmalonic acid (LIII), which was decarboxylated at its melting-point to an acid identical with the ß-(diphenyl-2)-propionic acid produced by hydrogenation of ß-(diphenyl-2)-acrylic acid (XLVIII).

After treatment of the acid chloride of XLII with aluminium chloride, the neutral product of ring-closure, purified by distillation, gave a crystalline ketone accompanied by oil. This ketone was isomeric with 3:4:5:6-dibenzcycloheptadiene-2-one (XXXIX), and gave an isomeric 2:4-dinitrophenylhydrazone; furthermore, oxidation of the ketone with warm alkaline permanganate

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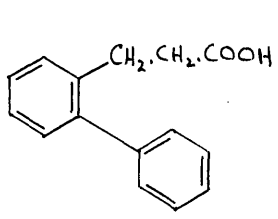
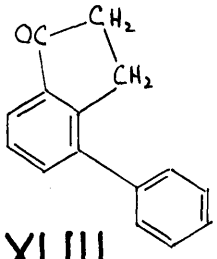
§§ This result is in conformity with the reported decomposition of N-nitrose-N-benzoyl-o-toluidine to benzpyrazole on heating in benzene (28); and with the decomposition of o-toluenediazonium hydroxide (29).

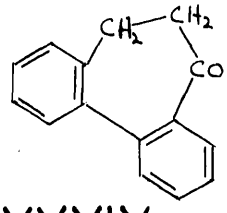
yielded 3-phenylphthalic acid (LV) which was characterised by analysis of its anhydride, and by ring-closure to fluorenone-1-carboxylic acid (LVI) identical with an authentic specimen. It follows that the ketone is 4-phenylhydrindone (XLIII). A portion of



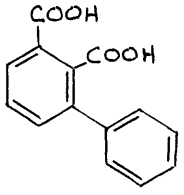
XLII



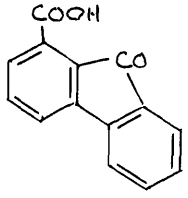
XLIII



XXXIX



LV



LVI

the residual gum, obtained from the crystallisation mother-liquors of this ketone, gave evidence of the presence of dibenz<u>cyclo</u>heptadiene-2-one, since on oxidation with sodium dichromate, phenanthraquinone and diphenic acid were isolated amongst the products; and the presence of XXXIX was substantiated when the crude dinitrophenylhydrazones, formed from this residual gum, furnished a small quantity of the 2:4-dinitrophenylhydrazone of 3:4:5:6-dibenz<u>cyclo</u>hepta-diene-2-one

(XXXIX) on fractional crystallisation. The semicarbazone of 4-phenylhydrindone (XLIII) melted at a temperature (225°- 229°/decomp.) considerably higher than that (192°) of von Braun's "sharp-melting semicarbazone", which may have been a mixture of isomerides. Quantitative separation of the ketonic mixture was not achieved but the amount of dibenzcycloheptadienone formed (as indicated by the yield of phenanthraquinone on oxidation) was certainly less than 15% of the mixture. Accordingly, whilst von Braun and Manz were mistaken in assuming that 4-phenylhydrindone is the only product of the ring-closure, it is formed in preponderating yield, and their conclusion still holds:

"Es folgt daraus also, daß der Hydrindenring leichter als der Benzosuberanring gebildet wird."

It is apparent that this method of ring-closure is not of general applicability as a synthetic route to the dibenzcycloheptadienes, though it might be possible to favour seven-membered ring-closure by suitable activation of the o'-position (in the second ring), or by deactivation or blocking of the 3-position (in the first ring), and others in this department are now engaged on this aspect of the synthesis.

In the meantime, preliminary work has indicated the feasibility of the fourth general synthetic route (p.25), in that certain phenanthrene derivatives appear to be capable of ring-enlargement to dibenzcycloheptadienes. For this reason the synthesis of 2:3:4:7--tetramethoxyphenanthrenes is now being undertaken in the hope that their subsequent ring-enlargement will provide 9:12:13:14-tetramethoxy-3:4:5:6-dibenzcyclohepta-3:5-dienes related to deaminocolchinol methyl ether (VIII).

INTRODUCTION - SECOND SECTION

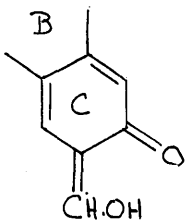
The first introductory section comprised a discussion of the reactions of the colchicine degradation products, derived from N-acetyliodocolchinol, wherein ring C is aromatic. In contrast to the considerable degree of assurance which attends the structures assigned to these degradation products, the structures of colchicine and colchiceine have not yet been clearly demonstrated, and the action of iodine and caustic potash on colchiceine, which causes aromatisation of ring C, has not been explained.

Investigation of the products of hydrolysis of colchicine has demonstrated that the alkaloid possesses one acetylated primary amino-group[5], three phenolic methoxyl groups[3], and another readily hydrolysable methoxyl group[7]. The analytical composition indicates that a sixth oxygen atom is present, but its function is not revealed by the reactions of the alkaloid[10]. These facts may be summarised in the formula $C_{16}H_9O.(OCH_3)_3.OCH_3.NHCOCH_3$.

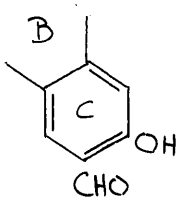
Under mild acidic[2] or alkaline[5] conditions,

colchicine, itself a neutral substance, is readily hydrolysed to methanol and colchiceine, which has fairly strong acidic properties and gives a characteristic enolic colour reaction with ferric salts. Further hydrolysis with concentrated mineral acid furnishes acetic acid and the free base "trimethylcolchicinic acid" - $C_{16}H_9O.(OCH_3)_3.OH.NH_2$ - which gives rise to two isomeric dibenzenesulphonyl derivatives - the isomerism being centred in the O-benzenesulphonic ester group since both isomers give, on partial hydrolysis, the same N-benzenesulphonyl derivative[7]. Windaus suggested that this isomerism could be regarded as a cis- trans- isomerism about the double bond in esters of a hydroxymethylene system; and, in view of the degradation brought about by iodine and caustic potash, he assigned to ring C in colchiceine the α-hydroxymethylene ketone structure LVII, since tautomerism to the o-hydroxyaldehyde structure LVIII could be followed by replacement of the aldehyde group by iodine. An analogous replacement has been observed in the case of ß-naphthol-α-aldehyde and salicylaldehyde[11], which colchiceine also resembles in its colour reactions and addition complexes with alkalis and acids[10].

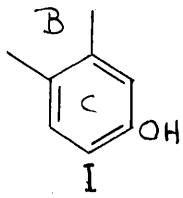
Furthermore, colchiceine, on bromination in acetic acid, furnished a compound which was apparently a tribromocarboxylic acid[9] and could conceivably have arisen by oxidation of an aldehyde grouping with simultaneous bromination.



LVII

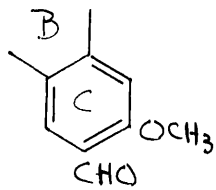


LVIII



I

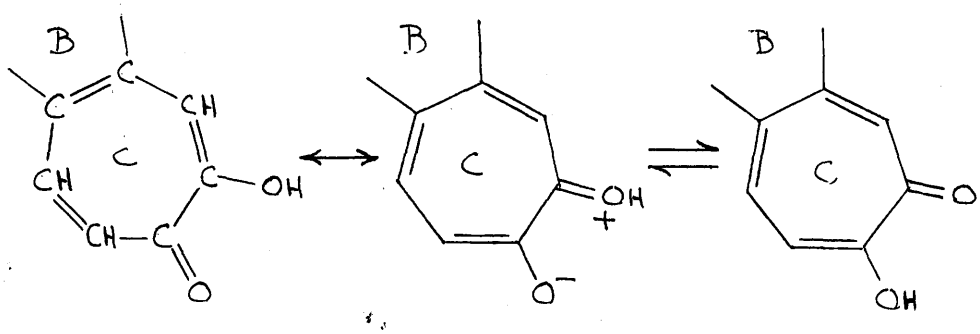
LIX



LX

The further implications of the structure LVII, however, are not borne out by the behaviour of colchiceine. A structure of this type would aromatise readily to the more stable salicylaldehyde structure LVIII, whose absence in colchiceine is indicated by the inertness to carbonyl reagents such as semicarbazide[10], and by the ultra-violet absorption spectrum (closely similar for both colchicine and colchiceine) which differs radically from that of N-acetylcolchinol methyl ether where the ring C is aromatic[31]. Moreover on methylation with ethereal diazomethane, colchiceine

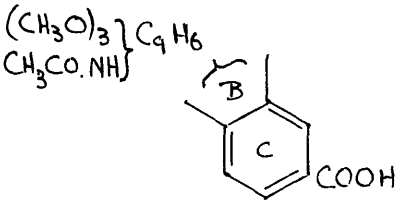
gives rise to two methyl ethers, colchicine and an isomeric substance iso-colchicine, and both isomers can be hydrolysed again to colchiceine with an ease which precludes the assignment to either of the phenol methyl ether structure LX. Accordingly the behaviour of colchiceine on methylation provides additional evidence of its failure to isomerise to an aromatic o-hydroxy aldehyde.



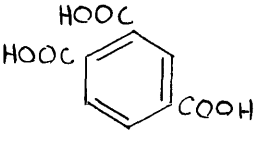
LXI LXII LXIII

An interesting alternative structure was advanced on theoretical grounds by Dewar[33], who suggested that ring C in colchiceine may possess a cycloheptatrien-ol-one or "tropolone" ring LXI, resonance with the "hybrid" LXII being postulated to account for the failure of the compound to show ketonic reactivity.

On this basis the existence of isomeric methyl ethers and benzenesulphonates can be explained if the parent enolone is assumed to be capable of the prototropic equilibrium LXI ⇌ LXIII. Dewar considers that "the facile conversion to benzene derivatives is due to benzilic acid rearrangement", though it is not clear how this would explain the degradation to the iodophenol structure LIX present in N-acetyliodocolchinol. On the other hand, such a rearrangement is probably implicit in the formation of an acid (formulated as LXIV on analytical grounds) when a solution of colchicine in methanol is heated with alkali methoxide or hydroxide,[34] and in the appearance of trimellitic acid (LXV) when colchicine is first fused with potassium hydroxide and then oxidised with permanganate[8] - the tribasic acid being most probably an oxidation fragment resulting from an aromatised ring C[§§].



LXIV



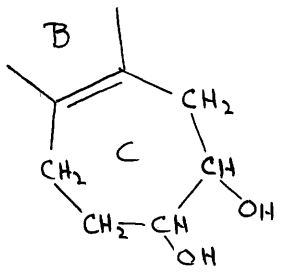
LXV

§§ Windaus, who discovered this degradation to the acid LXV, made the surprising suggestion (10) that the acid arose from the middle ring B.

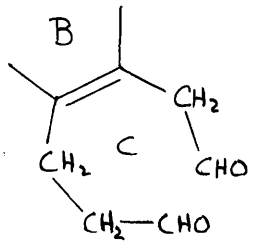
When colchicine and colchiceine are hydrogenated in the presence of Adam's platinic oxide, three moles of hydrogen are absorbed giving products where ring C is partially reduced. One (probably interannular) ethylenic linkage is retained - as shown by the formation of a crystalline ethylene oxide when hexahydrocolchicine is titrated with perbenzoic acid - and at the same time the "masked" carbonyl group suffers reduction to a detectable hydroxyl group[31]. Consequently hexahydrocolchiceine is a dihydric alcohol, formed on reduction of the ketone and of the enol groups. Greater stability towards rearrangement of the carbon skeleton, which is to be expected in this diol on account of its almost complete saturation, renders its further examination desirable in order to throw light on the structure of ring C; and indeed Dewar claimed to have demonstrated that the diol was an α-glycol, in that it underwent oxidation with lead tetraacetate. The oxidation product was not characterised but it showed carbonyl reactivity.[33] Recently, however, a short account[35] has appeared describing the oxidation of hexahydrocolchiceine with periodic acid, thereby indicating that the diol is an α-glycol in accordance with Dewar's formulation LXI§§.

§§ Windaus' structure LVII would, of course, lead to a 1:3 diol on hydrogenation.

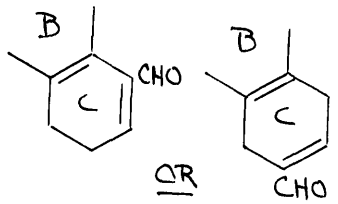
The crude oxidation product, which gave reactions characteristic of an aldehyde, furnished an amorphous dinitrophenylhydrazone. Analysis of the latter approximated to the calculated result for the dinitrophenylhydrazone of the mono-aldehyde $C_{21}H_{25}O_5N$, and the presumed oxidation mechanism is indicated in the formulae LXVI → LXVIII.



LXVI



LXVII



LXVIII

It may be noted in passing that the "tropolone" ring system, an original conception of Dewar's, was first suggested by him for the ring-structure of stipitatic acid (a metabolic product of the mould Penicillium stipitatum Thom)[36], and the same ring is now thought to be present in purpurogallin (an oxidation product of pyrogallol)[37], both of which products resemble colchiceine in several respects.

To summarise: The somewhat improbable structure LVII, suggested for ring C in colchiceine, has now collapsed under an accumulation of unfavourable evidence. An alternative "tropolone" structure XLI for this ring, appears to be capable of accomodating all the known facts, but rigid proof is lacking. The benzilic acid rearrangement has been suggested as a mechanism whereby the ring-system XLI could aromatise - such aromatisation being a feature of several reactions of colchiceine.

PART III SOME ATTEMPTS TO ELUCIDATE THE STRUCTURE OF COLCHICEINE AND HEXAHYDROCOLCHICEINE.

As a preliminary to an examination of certain degradation products of colchicine it was necessary to procure an ample supply of pure colchicine, and, in view of the cost and scarcity of the pure alkaloid, the commercially available crude Ext. Colchicum was utilised as a source. Separation of the main bulk of unwanted contaminants was based on the alkaloid's solubility in water and in chloroform, the purification procedure adopted being a modification of that advocated by Chemnitius[38], incorporating the chromatographic purification suggested by Ashley and Harris[39]. The aqueous solution of the crude extract was first extracted with paraffin wax to remove waxy impurities which otherwise, as preliminary investigation had shown, tend to retard and to survive the subsequent filtration from insoluble tars. This filtration - although still a tedious process - is notably accelerated by using much paper pulp. Exhaustive extraction of the aqueous filtrates with acid-free chloroform afforded a crude material of high colchicine content which was then

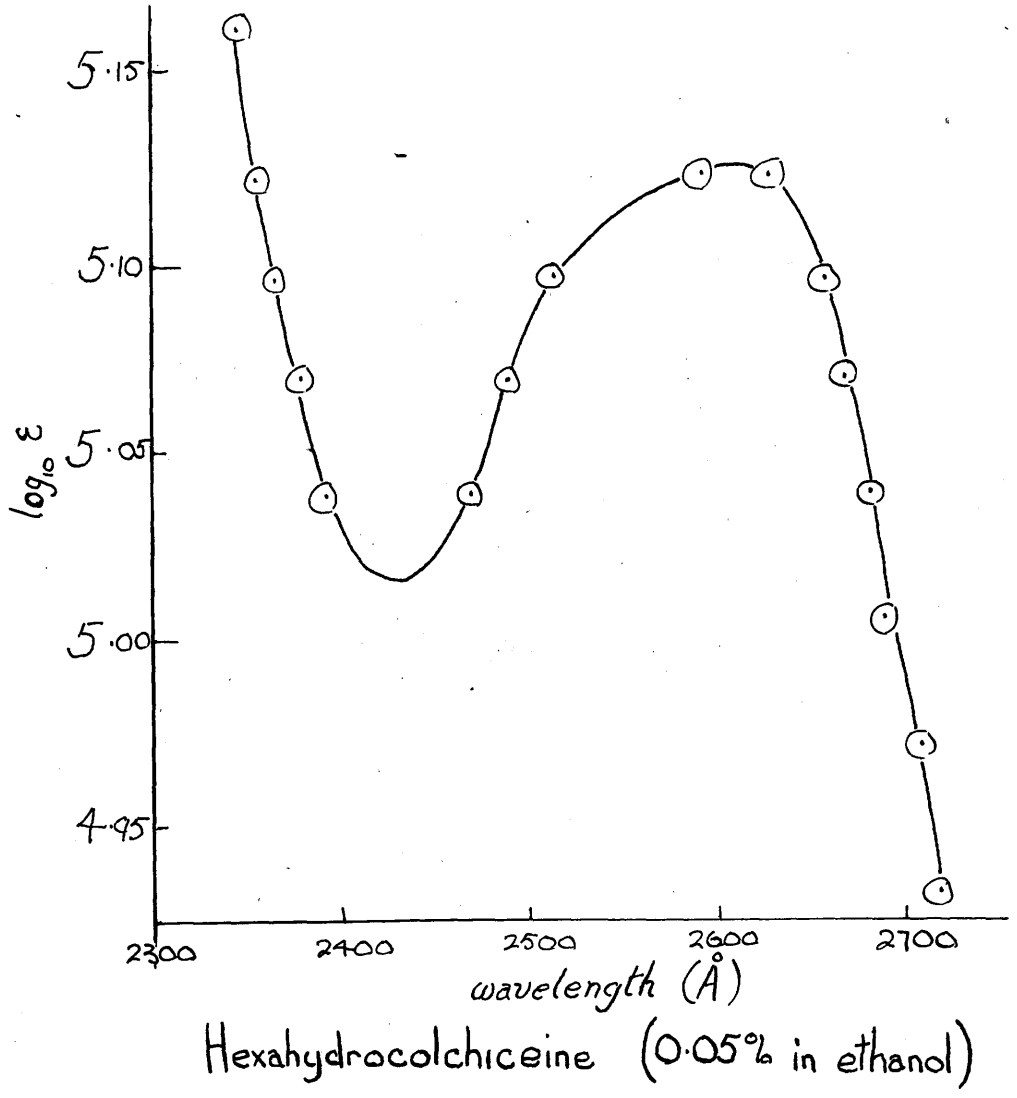
subjected to chromatography on alumina. The initial chromatogram effected a satisfactory separation from more strongly adsorbed impurities, but the colchicine was contaminated by a non adsorbed, green-coloured material (cf. Experimental). For degradative work it is desirable that the alkaloid be of good quality since it has been observed that impurities have a markedly adverse effect on both the yield and the purity of the colchiceine formed on hydrolysis. And, in fact, hydrolysis of a sample of the green-coloured colchicine indicated that impurities were present in sufficient amount to promote this undesirable effect, and that further purification was essential. Accordingly the material was adsorbed from a weaker solvent on freshly activated alumina in the hope that the rate of elution of the colchicine would be retarded sufficiently to allow the preceding green band to be separated from it. Under these new conditions, however, the expected green band did not appear, and the eluted colchicine was colourless: we are unable to account for this strange, but propitious disappearance of the colour. It was found, moreover, that the second chromatogram had separated two additional impurities which had previously

escaped detection because of the shortness of the original column. After removal of chloroform by repeated distillation with methanol[38] (in order to destroy the chloroform-colchicine complex[1]) pure, crystalline colchicine was obtained. The chromatographic by-products were separately eluted and retained.

Pure colchiceine, obtained by the customary hydrolysis of colchicine with dilute acid, was hydrogenated in the presence of Adam's platinic oxide. Hexahydrocolchiceine was obtained as the only crystalline product though in poor yield. It was found impossible to separate any of the contaminating by-products in the crude mixture remaining after evaporation of the crystallisation mother-liquors. The melting-points of the diol and of its diacetyl derivative agreed with those recorded by Bursian[31]. There is some discrepancy, however, in the analytical composition of the product, as compared with Bursian's analysis.

Hydrogenation of colchiceine with palladium black proceeded at a much slower rate, and the hydrogen uptake was less. The mixture of hydrogenation products did not yield any crystalline material. Chemical reduction of colchiceine with zinc and acetic acid, or with

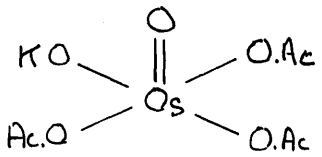
Raney-nickel alloy in dilute caustic soda solution, led, in each case, to intractable resinous material which could not be purified.



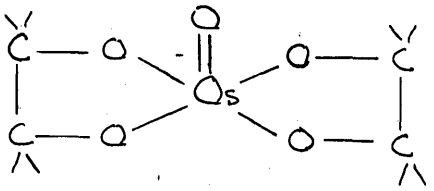
The ultra-violet absorption spectrum of hexahydrocolchiceine was examined, and found to show a marked

absorption maximum ($\varepsilon = 1.1 \times 10^5$) at a wavelength of 2580 Å (see graph). It was hoped that the absorption would indicate whether the remaining double-bond in hexahydrocolchiceine (compare p.40) was conjugated with the trimethoxybenzene nucleus A. For this purpose, however, it is necessary to compare the absorption spectrum with that of a compound possessing a similar structure, but without the double-bond. The best model for the purpose would be the fully saturated octahydride, and numerous attempts were made to hydrogenate hexahydrocolchiceine further. This was uniformly unsuccessful. Hydrogen was absorbed by only one sample of the diol, but even this absorption was attributable to the presence of impurity (cf. Experimental). On this account, critical appraisal of the absorption spectrum cannot be undertaken.

Criegee has recently described certain derivatives of osmium trioxide which form cyclic osmic esters with certain α-glycols. In the case of two of these reagents, namely potassium methyl osmiate - $(KO)_2.(CH_3O)_4.Os$ - and potassium triacetyl osmiate (LXIX), the formation of cyclic di-esters (LXX) is accompanied by a marked colour change in solution.



LXIX



LXX

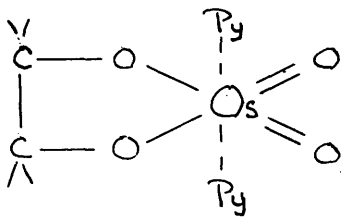
The colour reactions are given by diols only when the hydroxyl groups can take up a cis-1:2:configuration in space. Consequently acyclic 1:2:diols, cis-cyclopentane-, cis-cyclohexane-, and cis- and trans- cycloheptane-1:2:diols all give the reaction, but other diols are inert towards the reagents. When tested with the second reagent, hexahydrocolchiceine brought about a distinct positive reaction, which was shown to be a function of the diol groups (and to be unaffected by other parts of the molecule) in that the reaction no longer took place when the hydroxyls had been acetylated. Accordingly it would appear that the diol is a 1:2:glycol[§§]. Now such glycols may form cyclic esters

§§ It may be noted, in passing, that colchiceine gives a characteristic colour reaction with the reagents, in contrast to colchicine, salicylaldehyde, and benzoin (an α-ketol) which do not react (see Experimental).

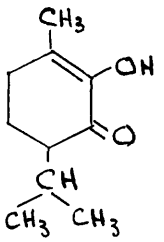
(usually crystalline compounds) with a third reagent described by Criegee. This reagent - a complex of osmium trioxide and pyridine ($OsO_3.2Py$) - gives so-called "mono-esters" (LXXI) with 1:2-diols, and the mono-esters can be hydrolysed back to the diol. Hexahydrocolchiceine appeared to enter into complex-formation with the reagent, but no crystalline ester could be obtained, and, on standing, metallic osmium was slowly deposited from the solution.

Oxidation of the diol with chromic anhydride in acetic acid led to a mixture of acidic and neutral materials which could not be obtained pure. With neutral potassium permanganate in acetone solution, the diol was slowly oxidised to a gummy acidic material.

An attempt to dehydrate ring C and simultaneously to deaminate ring B, by heating the hexahydride with phosphorus pentoxide in xylene, led only to gums which could not be brought to crystallise.



LXXI



LXXII

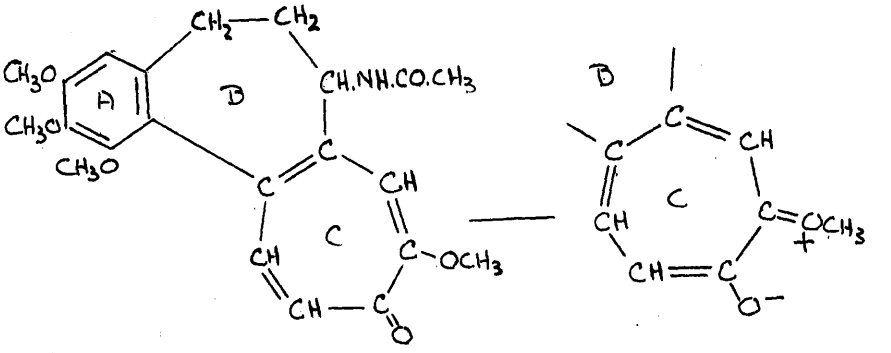
Wallach has shown that diosphenol (LXXII), which normally provides only a mono-oxime, can be induced to form a dioxime in strongly alkaline solution. Colchiceine was subjected to the conditions advocated by Wallach, to ascertain whether it could likewise be induced to oximate, but the colchiceine was recovered from the treatment unchanged.

In reviewing this section, in relation to its bearing on the problem of colchicine chemistry, only one fact merits consideration. The behaviour of hexahydrocolchiceine towards Criegee's reagents indicates that this hexahydride is a 1:2:diol. Such a formulation is in conformity with Dewar's hypothesis but in conflict with that of Windaus, (compare p.40).

CONCLUSION

No attempt has been made in the two introductory sections to give a comprehensive review of the chemistry of colchicine and its degradation products. The object has been rather to survey briefly those reactions on which structural considerations have been based, and so to provide a background for the fuller discussion of the present contribution to the field. The necessity for some degree of brevity must be the excuse for a didactical and somewhat uncritical approach.

It seems appropriate to conclude by giving an interim formula for colchicine itself. The formula LXXIII incorporates the most plausible structural features. It will be recalled that the cycloheptadiene structure for the middle ring B has not yet been confirmed in colchicine itself nor has the acetylamino-group been precisely localised; moreover the tropolone structure of ring C awaits rigid proof, and the positions of the keto- and methoxyl groups in that ring may need to be interchanged.

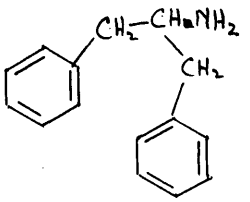

CH2—CH2
CH3O
CH3O
CH3O
A
B
CH.NH.CO.CH3
C
CH
C—OCH3
CH
CH—C
O
B
C
CH
C
CH
C=OCH3
+
CH=C
O−

LXXIII

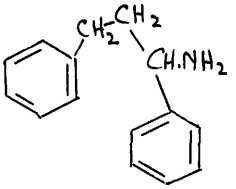
APPENDIX THE DEAMINATION OF CERTAIN N-ACETYLATED AMINES BY TREATMENT WITH PHOSPHORUS PENTOXIDE

It has already been noted (p.4) that, on heating in xylene with phosphorus pentoxide, N-acetylcolchinol methyl ether loses the elements of acetamide and is converted to the corresponding olefins, deaminocolchinol methyl ether (VIII) and iso-deaminocolchinol methyl ether (XIV, compare p.9). The same method of deamination was subsequently utilised in the case of the analogous degradation product N-acetyliodocolchinol methyl ether[43]. Moreover, 1-acetylamino-3:4:5:6--dibenzcyclohepta-3:5-diene was converted, by similar treatment, to 3:4:5:6-dibenzcyclohepta-1:3:5-triene (p.17). Only in the last case was the structure of the acetylated amine known with certainty, and it was desirable to examine the scope of the reaction in order to determine whether it was, in fact confined to N-acetylaminodibenzcycloheptadienes, to which class of compounds N-acetylcolchinol methyl ether and N-acetyliodocolchinol methyl ether probably belong (p.10). If the reaction were indeed applicable only to amines having a unique type of structure, then it would be of

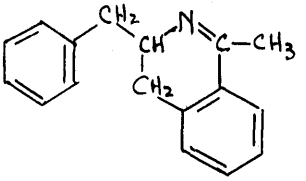
diagnostic value in testing unknown compounds for this structure. On the other hand, if the reaction were found to be of general applicability, it appeared to offer a convenient alternative to the tedious exhaustive methylation method of Hoffmann, as a means of effecting the deamination of primary amines.



LXXIV



LXXV



LXXVI

It was decided to extend investigation, in the first place, to the amino-1:3-diphenylpropanes (LXXIV and LXXV) which are the open-chain analogues of the cyclic aminodibenzcycloheptadienes. 2-Acetylamino--1:3-diphenylpropane was shown, by others in this department, to undergo deamination to 1:3-diphenylpropene on treatment with phosphorus pentoxide in xylene, although the main product of the reaction was the

dihydroisoquinoline LXXVI simultaneously formed by the more usual Bischler-Napieralski cyclisation§§.

The isomeric amine, 1-amino-1:3-diphenylpropane(LXXV) was prepared by a Leuckart reaction on dihydrochalkone,:-

$$Ph.CH_2.CH_2.CO.Ph + 2H.CO.NH_2 \longrightarrow Ph.CH_2.CH_2.CH(NH.CHO).Ph + NH_3 + CO_2$$

followed by hydrolysis of the resulting formyl derivative.(53) When the acetyl derivative, 1-acetylamino-1:3--diphenyl propane, was subjected to the phosphoric oxide treatment, 1:3-diphenylpropene (identified as the dibromide) was obtained in good yield.

Attention was now turned to amines unrelated structurally to those previously examined. Under the usual treatment in a preliminary trial, N-acetylcyclohexylamine gave evidence of deamination to cyclohexene. Since ample supplies of cyclohexylamine were available, this amine seemed to be a suitable case for systematic study of the reaction. Accordingly attempts were made to find a method for identifying cyclohexene in dilute solution in xylene. For this purpose the recorded methods of identification are excluded. Thus nitrosonitrate formation(45) requires pure cyclohexene, and the

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§§ A review of this reaction is given by Manske(44).

methoxyl-mercurial[46] is formed in methanolic solution.

Cyclohexene dibromide, however, is readily formed in the presence of xylene, and subsequently can be separated in a pure state, and so attempts were made to obtain a crystalline product derived from the dibromide and suitable for identification. Cyclohexene dibromide did not furnish a dithioether with either sodium p--thiocresate or 2:5-dichlorothiophenate. In each case the thiophenate was oxidised to the corresponding disulphide, sodium bromide being formed simultaneously. Presumably these reactions are analogous to the debromination of cyclohexyl bromide with sodium hydrogen sulphide[47]. Treatment of the dibromide with o--phenylenediamine also led to debromination. In view of these failures to obtain crystalline derivatives, a detailed study of the deamination of cyclohexylamine was not attempted.

A large-scale experiment with N-acetylcyclohexylamine, however, allowed partial fractionation of the products of phosphoric oxide treatment, and the low-boiling fraction was separated into cyclohexene (identified by oxidation to adipic acid) and acetonitrile (identified by reduction to ethylamine which was converted to the picrate and to 2:4-dinitrophenylethylamine).

The production of acetonitrile is worthy of note in that it accounts for all the nitrogenous material removed in the deamination - the yields of olefin and nitrile being almost identical (see Experimental). Indeed the dehydration of the acetylamino-fragment to the nitrile may be an important factor in the deamination reaction. In conformity with this suggestion is the observation that the free base 2-amino-1:3--diphenylpropane (see Experimental) and its tosyl derivative[§§] are unaffected by phosphorus pentoxide, whereas the acetyl derivative undergoes deamination (see above) - in the first two cases, removal of water from the nitrogenous substituent (NH_2- or $C_7H_7.SO_2.NH$-) is of course impossible.

In a further extension of the investigation it was found that neither N-acetylethylamine, nor N-acetyl--n-propylamine gave evidence of the formation of the corresponding olefins when heated with phosphorus pentoxide in xylene, although it was shown that the methods used to detect their presence were indeed capable of identifying both ethylene and propylene in small amount (see Experimental). In this connection

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§§ Unpublished work by Cook, Loudon, and collaborators.

a new method was elaborated to separate propylene by absorption in ethereal bromine, and identify it by conversion of the purified dibromide to propylene-bis--(2:5-dichlorophenyl)-disulphone.

Consequently, as a method of deamination of acetylamino-derivatives, the reaction is not generally applicable, but further work is necessary before it will be possible to delimit its scope.

EXPERIMENTAL

2:2'-Dibromomethyl-diphenyl (XXV)

A refluxing solution of 2:2'-ditolyl[48] (45.7g) in carbon tetrachloride (400cc) containing a trace of iodine and covered with a layer of water (100cc) was irradiated with three 40-watt filament lamps while a solution of bromine (84.4g) in carbon tetrachloride (150cc) was slowly added during two hours. After further refluxing (30 minutes), the cooled solution was washed with dilute caustic soda, dried, and concentrated. The product, which solidified on scratching with light petroleum, gave small colourless rhombs of 2:2'-dibromomethyl-diphenyl (from petroleum) m.p.89°-90°, yield 54%. (Kenner[19] gives m.p.87.5°; yield 41%).

3:4:5:6-Dibenzcyclohepta-3:5-diene-1--Carboxylic acid (XXX) and derivatives. (After Kenner[20])

Condensation of 2:2'-dibromomethyl-diphenyl with malonic ester and subsequent hydrolysis and decarboxylation gave dibenzcycloheptadiene-1-carboxylic acid (m.p.156° -157°) in 82% yield. The ethyl ester (b.p. 214° at 13mm) was obtained in 91% yield and converted to the hydrazide (m.p.174° -175°) in 86% yield

Urethane of 1-Amino-3:4:5:6-dibenzcyclohepta--3:5-diene (XXXI) (Modified from Kenner[20])

The above hydrazide was degraded by treatment with alcoholic nitrous acid, when concentration of the solution and crystallisation from benzene/petroleum yielded the urethane XXXI (m.p.85°-87°). The evaporated liquors from the crystallisation were refluxed for six hours with aqueous alcoholic caustic potash, and the concentrated result was separated by extraction into neutral, basic, and acidic fractions which were, respectively, more urethane (6% yield in all), 1-amino--dibenzcycloheptadiene hydrochloride (see below, yield 39%), and recovered dibenzcycloheptadiene-1-carboxylic acid (recovery 55%)

Kenner[20] records m.p.88° for the urethane.

3:4:5:6-Dibenzcyclohepta-3:5-dien-1-one (XXVIII) (After Kenner and Turner[19])

2:2'-Dicyanomethyldiphenyl (XXVI) (m.p.73°-76°) - formed in 63% yield on treating 2:2'-dibromomethyl-diphenyl with alcoholic potassium cyanide - underwent self-condensation on treatment with ethanolic sodium ethoxide to give 1-imino-2-cyano-3:4:5:6-dibenzcyclo-heptadiene (XXVII) (m.p.187°-188°) in 82% yield.

The latter was hydrolised on standing in concentrated sulphuric acid solution to 1-imino-3:4:5:6-dibenzcyclo-heptadiene-2-carboxylic acid (m.p.182°-184°) in theoretical yield, and this imino-acid gave an 86% yield of 3:4:5:6-dibenzcycloheptadien-1-one (m.p.77°) on refluxing in 50% sulphuric acid. The oxime melted at 187° -189°. All m.p.s agree with those recorded by Kenner and Turner[19].

3:4:5:6-dibenzcyclohepta-3:5-dien-1-one 2:4-dinitrophenylhydrazone gave orange needles m.p.199°-200° from glacial acetic acid. (Found; C, 65.1; H, 4.1; $C_{21}H_{16}O_4N_4$ requires: C, 64.9; H, 4.1%)

1-Amino-3:4:5:6-dibenzcyclohepta-3:5-diene (XXXII)

(a) The corresponding urethane was hydrolised by heating in a sealed tube with concentrated hydrochloric acid (10 parts by weight) at 150° for six hours.

Alternatively the hydrolysis was effected by six hours' refluxing with concentrated aqueous-alcoholic caustic potash.

(b) The dibenzcycloheptadiene-1-ketoxime (0.82g) in ethanol (100cc) was hydrogenated in the presence of Raney nickel at 85°/64 atmospheres. The base was

precipitated as the picrate from the ethereal solution of the concentrated filtrates, and recovered in ether by washing with alkali to remove picric acid.

In each case the base gave an hydrochloride as colourless needles m.p.256°-258° from dilute hydrochloric acid. (Found: C,73.4; H,6.7; Calc. for $C_{15}H_{16}NCl$: C,73.3; H,6.5%.)

On shaking with acetic anhydride and dilute caustic soda, the base was converted to the N-acetyl derivative which crystallised in colourless needles m.p.157° -158° from aqueous ethanol. (Found: C,81.1; H,6.7; Calc. for $C_{17}H_{17}ON$: C,81.3; H,6.8%)

Kenner records m.p.287° for the hydrochloride, and m.p.147° for the N-acetyl derivative.

Deamination of 1-Aminodibenzcycloheptadiene (XXXII)

(a) The corresponding N-acetyl derivative (3.1g) in pure dry xylene (75cc) was heated under reflux for half-an-hour with phosphorus pentoxide (10g). Distillation of the concentrated xylene filtrates gave 3:4:5:6-dibenzcyclohepta-1:3:5-triene (XXXIII) (68% yield) as a colourless mobile oil b.p.100°-110° (air bath temp.)/10 mm. (Found: C,93.6; H,6.4; $C_{15}H_{12}$ requires C,93.8; H, 6.3%).

Microhydrogenation with palladium black in acetic acid showed a hydrogen absorption equivalent to 0.85 double bonds. The triene displayed no evidence of picrate formation when treated with picric acid in ethanol. With bromine in acetic acid solution it furnished a dibromide (obtained by dilution of the acetic acid and extraction with ether) as colourless needles m.p.90°-91° from methanol. (Found: C,51.1; H,3.5; $C_{15}H_{12}Br_2$ requires C,51.2; H,3.4%).

On one occasion, a higher-boiling fraction (b.p. 145° at 0.2mm) was obtained as the main product of the deamination. The product gave colourless platelets from acetic acid. (Found; C,92.6; H,7.3%), and was saturated towards bromine. It cannot however be dibenzcycloheptadiene since the m.p. of the latter is 52°(49). (Calc. for $C_{15}H_{14}$: C,92.8; H,7.3%)

(b) The corresponding urethane (1g) was refluxed in xylene (65cc) with phosphorus pentoxide (4g). The concentrated xylene filtrates furnished unchanged starting material on rubbing with petroleum. Evaporation of the petroleum liquors gave a semi-solid which was washed with ethanol, leaving an unidentified material which crystallised in colourless needles from

2-ethoxyethanol m.p.322°-325° (with sublimation). (Found: C,83.2; H,6.2; N,5.8%; P absent). The concentrated ethanol washings from this material gave, on fractional distillation, a small amount of the triene (identified as the above dibromide m.p. and mixed m.p.89°-90°) and some more starting material (recovery 57% in all)

(c) The hydrochloride was heated in a sublimation apparatus at 320°(bath temp; at 300° the compound slowly sublimes unchanged). The sublimate was taken up in ether, washed with dilute hydrochloric acid (which removed unchanged hydrochloride) dried, concentrated, and distilled under reduced pressure, when the bulk of the material distilled between 80° and 115° (air bath temp.)/0.1mm as an oil from which crystals separated. The latter were identified as 9-methylphenanthrene (m.p. and mixed m.p.91°; picrate m.p. and mixed m.p.152°-153°) and the oil was shown to contain dibenzcycloheptatriene by conversion to the dibromide m.p. and mixed m.p.87°-90°. A small higher-boiling fraction (b.p.175° -185°/0.2mm) was not investigated further, beyond noting that it did not yield a picrate in ethanol.

Thermal Decomposition of Barium 3:4:5:6--Dibenzcyclohepta-3:5-diene-1-carboxylate

The barium salt, containing some un-neutralised barium hydroxide, was heated under reduced pressure. A yellow viscous oil slowly distilled at 170°-200° (bath temp.) at 10mm and solidified in the receiver. After purification by chromatography, this yielded colourless needles m.p. and mixed m.p. with 9-methylphenanthrene 90°-91°, the picrate had m.p. and mixed m.p. 153°-154°.

Oxidation of 3:4:5:6-Dibenzcyclohepta-1:3:5-triene

(a) With sodium dichromate

The triene XXXIII (0.3g) in acetic acid (1.6cc) was treated with sodium dichromate (0.98g) in acetic acid (2.3cc) and the solution was heated for one and a quarter hours at 100°. After dilution, a chloroform extract of the mixture was washed with dilute sodium carbonate, dried, and concentrated. The residue, dissolved in benzene-petroleum (1:1) was separated on a column of alumina into a feebly adsorbed pale-pink band and a more strongly adsorbed orange band. The

eluate of the former gave, on evaporation, a gum which solidified on scratching with petroleum, yielding 3:4:5:6-dibenzcyclohepta-1:3:5-trien-7-one (XXXVIII) m.p.83°-84° from benzene/petroleum. (Found: C,87.4; H,4.9; $C_{15}H_{10}O$ requires C,87.4; H,4.9%). Microhydrogenation with palladium black gave 0.98 double bond. The ketone gave a 2:4-dinitrophenylhydrazone as crimson rosettes m.p.231°-232° from acetic acid. (Found: C,65.3; H,3.6; $C_{21}H_{14}O_4N_4$ requires C,65.3; H,3.6% and dissolved in strong sulphuric acid to a bright yellow solution.

The orange band was eluted with benzeneethanol from which was recovered phenanthraquinone, m.p. and mixed m.p. 200°-202° from benzene (the diazine, formed on reaction with o-phenylenediamine, had m.p. and mixed m.p.218°, from glacial acetic acid). The carbonate washings of the chloroform extract gave, on acidification, phenanthrene-9-carboxylic acid m.p. and mixed m.p.249° -251°(after sublimation and crystallisation).

(b) With Selenium Dioxide

A solution of the triene (0.19g) in xylene (1cc) was heated under reflux with selenium dioxide (0.125g) for six hours. The gum obtained from the filtered and concentrated solution was dissolved in ether, washed

with dilute sodium hydroxide, then with water, dried, recovered, and distilled. Dibenzcycloheptatrien-7-one was obtained as a yellow oil, b.p.115°(bath-temp.)/0.2 mm, which solidified in the receiver, m.p. and mixed m.p. with the above sample 83°-84°.

(c) With osmium tetroxide.

A solution of the triene (0.5g) in dry ether (25cc) was treated with osmium tetroxide (0.75g) in dry ether (25cc). After 3 days, the residue obtained by removing the solvent was heated under reflux with a solution of hydrated sodium sulphite (8g) in water (75cc) and methanol (100cc) for 3 hours. Undissolved solid was collected and well washed with methanol, filtrate and washings being combined and concentrated. The concentrates were diluted with water and extracted with ether from which, after further washings with water and drying, the product was recovered. cis-1:2-Dihydroxy--3:4:5:6-dibenzcycloheptа-3:5-diene (XXXV) formed colourless prisms, m.p.121° from methanol (Found: C,79.8; H,6.3; $C_{15}H_{14}O_2$ requires C,79.7; H,6.2%).

Scission with lead tetra-acetate.

Lead tetra-acetate (120mg) was added, portionwise and with shaking, to a solution of the above diol (60mg) in pure dry benzene (18cc) maintained at 40°. The mixture was heated to boiling and then left at room temperature for 1 hour. After filtration the benzene solution was washed with water, dried, and evaporated. The resulting gum, which did not crystallise from ethanol, slowly deposited pale yellow needles of 9-phenanthraldehyde after being warmed with a little sodium carbonate in ethanol. The aldehyde had micro-m.p.99°-100° (positive test with 2:4-dinitrophenyl-hydrazine), and was oxidised by dropwise addition of 6% potassium permanganate (0.3cc) to its solution (11mg) in pure acetone (1cc). After clarification with sulphurous acid, the solution was extracted with chloroform from which phenanthrene-9-carboxylic acid, m.p. and mixed m.p.245°-248°, was recovered by means of aqueous sodium carbonate and was purified by vacuum sublimation. The chloroform residues contained some unchanged aldehyde.

Conversion of 3:4:5:6-Dibenzcyclohepta-1:3:5--triene (XXXIII) to 9-methylphenanthrene

A solution of the triene (0.16g) in acetic acid (4.2cc) and hydriodic acid (1.5cc; d 1.7) was heated under reflux for 4 hours. The oil obtained by evaporation was saturated towards bromine and contained (non-ionic) iodine. Since attempted purification by distillation in a vacuum caused liberation of iodine, the crude material was used in two portions:

(a) Chromatography gave no evidence of the presence of 9-methylphenanthrene at this stage, but, when the eluted and recovered material was distilled from sodium ethoxide, the distillate consisted of almost pure 9-methylphenanthrene, m.p. and mixed m.p. 90°-92°.

(b) When the oil was mixed with zinc dust and distilled at atmospheric pressure, much charring ensued; the distillate, which contained only a little solid, was again mixed with zinc dust, heated at 260° for several hours, and re-distilled. The product was a pale yellow oil, b.p. 90°-100° (air bath)/10mm, of which the later portion solidified and was separately crystallised from methanol giving 9-methylphenanthrene, m.p. and

mixed m.p. 89°-90° (picrate, m.p. and mixed m.p.153°-154°). The earlier oily portion of the distillate was saturated towards bromine and was analysed after renewed distillation in which only the first runnings were taken (Found: C,92.9; H,6.8; Calc. for $C_{15}H_{14}$: C,92.8; H,7.2%). It was possibly dibenzcycloheptadiene

Oxidation of 3:4:5:6-Dibenzcyclohepta-3:5:dien-1-one (XXVIII)

(a) With Sodium Dichromate

The ketone (0.2g) in warm acetic acid (1cc) was treated with a solution of sodium dichromate (0.9g) in water (1cc) and acetic acid (1cc). After gentle refluxing for one hour, the cooled solution was diluted, and extracted with chloroform which was washed with dilute caustic soda, dried and concentrated. The residue gave yellow platelets m.p. and mixed m.p. 204°-205°(from benzene). The phenazine from o-phenylene diamine had m.p. and mixed m.p. 218°-219°. The alkaline washings gave white platelets m.p. and mixed m.p. with diphenic acid 220° -222°(from ethanol).

(b) With Selenium Dioxide

The ketone (0.2g) with selenium dioxide (0.11g) was warmed with acetic anhydride (0.2cc) at 80° for four hours. On diluting with glacial acetic acid a crystalline product separated and was filtered. On attempting to crystalline from acetic acid or benzene, however, the material progressively decomposed to a red glassy resin, from which, after standing for some days, a small amount of phenanthraquinone separated (m.p. and mixed m.p. 195°-200°).

3:4:5:6-Dibenzcyclohepta-3:5-diene-2-one (XXXIX)

The unsaturated ketone (XXXVIII, 0.17g) in acetic acid (7cc) was hydrogenated with palladium black (0.05g) as catalyst, the absorption being complete in 45 minutes at room temperature. After removal of the solvent from the filtered solution, 3:4:5:6-dibenzcyclohepta--3:5-dien-2-one (XXIX) was obtained as pale-yellow hexagonal prisms m.p.85°-86° from benzene/petroleum (m.p. depressed to 55°-75° on admixture with starting material). (Found: C,86.5; H,5.7. $C_{15}H_{12}O$ requires C,86.5; H,5.8%). The 2:4-dinitrophenylhydrazone

crystallised in lustrous orange needles m.p.240°/decomp. (Found: C,65.1; H,4.1; $C_{21}H_{16}O_4N_4$ requires C,65.0; H,4.1%)

The ketone (115 mg) was oxidised by adding a solution of sodium dichromate (0.5g) in acetic acid (1.5cc) to its solution in acetic acid (1cc) and subsequent heating under reflux for one hour. After dilution with water, extraction with chloroform, and washing of the extract with sodium hydroxide, the recovered neutral fraction was identified as phenanthraquinone m.p. and mixed m.p. 202°-204° from benzene (diazine m.p. and mixed m.p. 218°-220°). Acidification of the alkaline washings gave diphenic acid, m.p. and mixed m.p. 210°-215° from ethanol.

Diphenyl-2-aldehyde from Diphenyl-2-carboxylic acid.

Methyl diphenyl-2-carboxylate (b.p.167°at 16mm) was prepared from diphenyl-2-carboxylic acid[50]. The methyl ester (14.8g), on heating under reflux with hydrazine hydrate (25g of 98%) and ethanol (30cc) for five hours, was converted in 72% yield, to the hydrazide (XLV) of diphenyl-2-carboxylic acid, which gave colourless needles (from methanol) m.p.136.5°. (Found: C,73.8; H,5.6; $C_{13}H_{12}ON_2$ requires: C,73.6; H,5.7%)

A cooled and stirred solution of the hydrazide (9.6g)

in pyridine (40cc) was slowly treated with benzenesulphonyl chloride (8.2g), and then left at room temperature for three hours. After removal of pyridine by trituration of the mixture with ice and dilute hydrochloric acid, the filtered orange solid was washed with acid and water and then dried. Crystallisation from methanol furnished the benzenesulphon-hydrazide (XLVI) of diphenyl-2-carboxylic acid (colourless needles) in 90% yield; m.p.173.5° (Found: C,64.8; H,4.6; $C_{19}H_{16}O_3N_2S$ requires: C,64.8; H,4.6%)

A solution of the sulphonhydrazide (14.3g) in ethylene glycol (70cc) was well stirred at 160°. Sodium carbonate (21g) was rapidly added, and, 80 seconds thereafter, the reaction was quenched by pouring the mixture into hot water. An ether extract of this solution was concentrated. The residue distilled at 162°/12mm as pale yellow oil. The yield of distilled Diphenyl-2-aldehyde was 77%.

ß-(Diphenyl-2)-acrylic acid (XLVIII)

Diphenyl-2-aldehyde (5.6g) and malonic acid (6.2g) were heated together in solution in dry pyridine (10cc)

containing some dry piperidine (0.5cc) at 100° for one hour, and then at the boiling-point for half-an-hour. The crude acid obtained on triturating the mixture with ice and dilute hydrochloric acid, was filtered and washed. ß-(Diphenyl-2)-acrylic acid gave colourless needles (from aqueous acetic acid). After drying at 100° under reduced pressure m.p. was 195°-196°. (Found: C,80.2; H,5.5; $C_{15}H_{12}O_2$ requires: C,80.4; H, 5.4%). Yield 89%.

Soon after this acid had been prepared a paper by Zaheer and Faseeh[51] came to hand. They give the m.p. of this acid as 202°.

ß-(Diphenyl-2)-propionic acid (XLII)

The unsaturated acid (6.2g) in glacial acetic acid (450cc) was hydrogenated at room temperature using palladium black (0.3g) as catalyst. The hydrogen absorption (about 1 mole) was complete in two and a half hours. After distillation of the solvent from the filtered solution, the residual acid (93% yield) gave white plates m.p.110° -113° (from aqueous acetic acid, or benzene and petroleum), and was insoluble in water.

The acid was methylated with diazomethane in ether, and, after removal of the ether, the residue distilled at a constant temperature 181.5°-182° at 10mm. to furnish methyl ß-(diphenyl-2)-propionate as a colourless oil. (Found: C,80.1; H,6.5; $C_{16}H_{16}O_2$ requires: C,80.0; H,6.7%). Hydrolysis of the methyl ester with boiling aqueous-ethanolic potassium hydroxide, gave back ß-(Diphenyl-2)-propionic acid m.p. 112.5°-113°. (Found: C,79.8; H,6.0; $C_{15}H_{14}O_2$ requires: C,79.7; H,6.2%).

Von Braun and Manz[25] describe the acid as melting at 125° after crystallisation from water.

α-(o-Tolyl)-γ:γ-dimethyl triazen.

A solution of o-toluidine (32.1g) in concentrated hydrochloric acid (108cc) and water (72cc) was chilled, and the suspension treated, at 0°, with a solution of sodium nitrite (21g) in water. The cold diazonium solution was added slowly to a stirred, ice-cold solution of dimethylamine (48g of 33%solution) in aqueous sodium carbonate (150g). The dried (potassium hydroxide) benzene extract was concentrated and α-(o-tolyl)-γ:γ--dimethyl triazen (XLIX) (92% yield) distilled at

128°-129° at 12mm as a mobile pale-yellow oil. (Found: C,66.1; H,7.8; $C_9H_{13}N_3$ requires: C,66.3; H,8.0%).

2-Methyldiphenyl

Glacial acetic acid (40cc) was slowly added (over four hours) to a refluxing solution of the triazen (45g) in benzene (400cc), and left boiling under reflux overnight. The solution was well washed with warm water, dilute acid and then dilute alkali. The dried (caustic potash) benzene solution was concentrated and subjected to distillation under reduced pressure. (52) 2-Methyldiphenyl distilled at 128°-130° at 15mm (leaving a considerable non-volatile residue) and was purified by re-distillation. (Yield 9%). The acid washings of the reaction mixture yielded benzpyrazole (21% yield) on neutralisation. Recrystallisation from ligroin gave white needles m.p.144°-145°. (Found: C,71.5; H,5.0; N,23.8; Calc. for $C_7H_6N_2$: C,71.2; H,5.1; N,23.7%). The alkaline washings appeared to contain much o-cresol.

2-Bromomethyldiphenyl

A gently boiling solution of 2-Methyldiphenyl (4.1g)

in carbon tetrachloride (25cc), containing a trace of iodine, and covered with a layer of water (6cc) was strongly irradiated with visible light while a solution of bromine (4.1g) in carbon tetrachloride (12cc) was slowly added during two hours. After further refluxing (half-an-hour) the cooled solution was washed with sulphurous acid, dilute sodium carbonate, and water, and dried and concentrated. 2-Bromomethyldiphenyl (65% yield) distilled at 168° -172° at 11mm as a pink mobile oil. (von Braun[25] gives b.p.166°/12mm.)

o-Phenylbenzylmalonic ester.

Malonic ester (2.8g) in absolute ether (45cc) was rapidly run into a stirred, refluxing solution of sodium (0.4g) in absolute ethanol (5cc), and thereafter 2-bromomethyldiphenyl (4.3g) in absolute ether (40cc) was added during half-an-hour. After further boiling for three hours, the washed (water) and dried ether solution was concentrated and distilled under reduced pressure. Malonic ester (20% recovered) and bromomethyldiphenyl (35% recovered) first distilled, followed by diethyl o-phenylbenzylmalonate (39% yield) which distilled at 124° -125° at 12mm as a viscous, pale-yellow oil (von Braun[25] gives b.p. 124° -124°/12mm

o-Phenylbenzylmalonic acid (LIV)

The diethyl ester was hydrolysed with boiling aqueous-ethanolic potassium hydroxide. After removal of the alcohol the diluted solution was extracted with ether (which removed some neutral material) and acidified. The precipitated oil was boiled with much water, whereby some dissolved, and from this solution o-phenylbenzyl-malonic acid crystallised (after some days) in white needles which melted (with gas evolution) at 125.5° - 127.5°, and after cooling re-melted at 108°-110°. (After drying at 65° under reduced pressure, Found: C,71.1; H,5.1; $C_{16}H_{14}O_4$ requires: C,71.1; H,5.2%)

The acid was heated at 130° until evolution of carbon dioxide had ceased. After crystallisation from benzene/petroleum, the product gave needles m.p.111° - 113° not depressed by admixture with ß-(diphenyl-2)--propionic acid prepared by reduction of ß-(diphenyl-2)--acrylic acid (p.74).

Ring closure of ß-(diphenyl-2)-propionic acid (XLII)

The acid (2g) in suspension in pure dry benzene (20cc) was treated with phosphorus pentachloride (2g), shaken (with moisture guard) until solution of the acid

was complete, and then left standing for one hour. The acid chloride, remaining after evaporation under reduced pressure, was taken up in dry carbon disulphide (4cc), powdered fresh aluminium chloride (3g) was added, and the whole was then left for three days at 0°. Dilute hydrochloric acid was added, the solvent was removed by steam distillation, and the resultant liquors were extracted with ether, which was washed with caustic soda (giving a negligible amount of acidic gum on neutralisation), dried, and evaporated. The residue distilled at 130°-135° at 10mm (75% yield), and crystallised in the receiver. Crystallisation from aqueous ethanol gave rectangular prisms of 4-Phenylhydrindone (XLIII) (45% yield) m.p.69° (depressed to 43°-50° by admixture with 3:4:5:6-dibenzcyclohepta-3:5-diene-2-one (XXXIX). (Found C,86.7; H,5.6; $C_{15}H_{12}O$ requires: C,86.5; H,5.8%) 4-Phenylhydrindone furnished a 2:4-dinitrophenylhydrazone "A" (scarlet needles from acetic acid) m.p.243°-245°/ decomp., depressed to 216° -220° by admixture with the dinitrophenylhydrazone of dibenzcycloheptadiene-2-one (XXXIX) (Found: C,65.1; H,4.3; $C_{21}H_{16}O_4N_4$ requires: C,65.0; H,4.1%). The semicarbazone of 4-Phenylhydrindone

gave white platelets insoluble in water, alcohol, or acetone but crystallisable from ß-ethoxyethanol; m.p.225°-229°/decomp. (Found: C,72.3; H,5.6; N,15.7; $C_{16}H_{15}ON_3$ requires: C,72.5; H,5.7; N,15.9%).

The mother-liquors from the crystallisation of 4-Phenylhydrindone gave, on evaporation, a non-crystalline gum. This was treated in two portions:-

(i) The gum (0.3g) in glacial acetic acid (3cc) was treated with sodium dichromate (1.3g) in acetic acid (3.5cc) and the solution was refluxed for one hour. A chloroform extract of the diluted solution was washed with caustic soda, dried, and concentrated. The gummy neutral residue gave crystals of phenanthraquinone (from chloroform), m.p. and mixed m.p. 204° -205°. The phenazine from o-phenylene diamine had m.p. and mixed m.p. 220° -221°. The alkaline liquors gave, on acidification, diphenic acid, m.p. and mixed m.p.216°-219°.

(ii) The gum (0.28g) was treated with 2:4-dinitrophenylhydrazine (0.3g) in ethanolic sulphuric acid, and the well-washed precipitate was taken up in the minimum volume of hot acetic acid. The dinitrophenylhydrazone "A" (mixed m.p. 243°/decomp.) crystallised on cooling

and the filtrate, on standing overnight, deposited a very small amount of a second dinitrophenylhydrazone (m.p. 230° -233°/decomp. depressed to 220° -226°/decomp. by admixture with A). The liquors were concentrated by half, and, when cold, seeded with A. The resultant crystals (slightly impure A) were filtered after two hours, the filtrate being then seeded with the second dinitrophenylhydrazone, whereupon more of the second compound came out of solution. Repeated recrystallisation of the latter gave red-orange needles m.p.236°-238°/decomp., raised to 238°-240°/decomp. by admixture with the dinitrophenylhydrazone of dibenzcycloheptadiene--2-one (XXXIX), and depressed to 216° -224°/decomp. by admixture with A. Seeding of the liquors in the order opposite to that indicated gave only a mixture of the two dinitrophenylhydrazones (m.p. 220° -230°/decomp.)

A preliminary test showed that the two dinitrophenylhydrazones, after mixing, could not be separated on a column of alumina, and hence no quantitative separation was attempted.

Oxidation of 4-phenylhydrindone

A well-stirred emulsion of the ketone (0.2g) in a

little dilute caustic soda at 100° was treated portion-wise with aqueous (6%) potassium permanganate until the pink colour persisted. Excess permanganate (2cc) was now added and the whole left for one hour at 100°. The acidified mixture was "clarified" with sulphur dioxide and the insoluble acidic material was filtered, well washed with water, dissolved in alkali, and re-precipitated. On sublimation (120° at 2mm) this acidic material furnished 3-Phenylphthalic anhydride (colourless prisms from benzene/petroleum) m.p.145°. (Found: C,74.9; H,3.5; $C_{14}H_8O_3$ requires: C,75.0; H,3.6%) Hydrolysis of the recrystallised anhydride gave 3-phenyl-phthalic acid m.p.169° -171°(30).

The acid was cyclised by warming for ten minutes in concentrated sulphuric acid at 50°. Subsequent dilution with water yielded fluorenone-1-carboxylic acid (orange needles from aqueous ethanol) m.p. and mixed m.p.190° -191°.

Purification of Colchicine

A concentrated extract of Colchicum autumnale (specified to contain 4.3% of colchicine) was supplied by Messrs. Ransom of Hitchin, Herts. The crude extract (426g) diluted with water (600cc) was twice extracted

(when hot) with paraffin wax (100g each time) which extracted some green colour. The combined wax layers were well washed with boiling water and the combined aqueous solutions, after thorough mixing with acid-free paper pulp (70g), were filtered through a "pre-coat" of pulp (10g). The filter-bed was well washed with water, churned up with boiling water and refiltered through a fresh pre-coat, these washings being added to the bulk of the filtrate. The clear, deep-brown filtrate was then thoroughly extracted with acid-free chloroform (5 litres in twenty lots), and the partly concentrated chloroform extract was dried with potassium carbonate and evaporated to a dark-brown syrup. This crude material was taken up in dry acid-free chloroform (150cc) and passed on to a column of alumina (B.D.H. "Alumina for Chromatography") measuring 23 cm.by 3.5 cm. and saturated with benzene. On developing the chromatogram with chloroform, the following bands were noted (in the order of increasing adsorption):-

(i) Narrow, bright-green band co-inciding with the benzene/chloroform interface,

(ii) Broad pale-green band,

(iii) Colourless region,

(iv) Band fluorescing pink in ultra-violet light,

(v) Broad yellow band,

(vi) Narrow crimson band,

(vii) Narrow brown band (top of column)

Bands (i), (ii), and (iii), were too close together to admit of satisfactory separation, and their mixed eluates were collected together. The extruded column was manually separated into its component bands. Bands (iv), (v), and (vi) were eluted with methanol, and band (vii) with methanolic ammonia, and the concentrated eluates were retained.

The mixed eluates of bands (i), (ii), and (iii) were evaporated to dryness and taken up in a one-to-one mixture of acid-free chloroform and peroxide-free ether, and re-chromatographed on a similar column of alkali-free alumina, newly activated by heating under reduced pressure (280° at 10mm) for one hour. The column, developed with the same ether/chloroform mixture, gave bands distinguished by their fluorescence in ultra-violet light:-

(viii) Lower pale-yellow band, fluorescing yellow-green,

(ix) Middle, pink-fluorescing band,

(x) Upper, yellow-fluorescing band.

No lower bright-green band appeared on this column. Band (viii) was eluted with chloroform until the eluate gave no further residue on evaporation, and the concentrated eluate was freed from chloroform by repeated distillation with methanol. The residual pale-yellow gum gave minute needles of pure colchicine (from ethyl acetate) m.p. 149°-150°. Yield 13.3g.

The second column was extruded and the component regions were separated. The band (viii) still fluoresced faintly and, after elution with methanol, furnished a little (2g) more colchicine, m.p. 149°-150°. Bands (ix) and (x) were separately eluted with methanol and the concentrated eluates were retained.

Colchiceine

Pure colchicine (7.4g) was gently boiled with dilute hydrochloric acid (30cc of concentrated acid, in 450 cc water) for two hours. The clear solution, on standing, deposited colchiceine (80% yield), and more colchiceine was obtained from the filtrates by chloroform extraction. Colchiceine gave almost colourless needles of the hydrate (m.p.145° -150°) from aqueous methanol. Anhydrous colchiceine gave pale-yellow needles (from dioxan/ether), m.p. 178°.

Hexahydrocolchiceine

Colchiceine (3.5g) in glacial acetic acid (40cc) was hydrogenated at room temperature using platinic oxide (0.2g) as catalyst, the hydrogen absorption (3.7 moles) being complete in four hours. After distillation of the solvent from the filtered solution, the residue was dissolved in ethyl acetate and furnished colourless needles of hexahydrocolchiceine m.p.201°-202° (after recrystallisation). The mother liquors deposited further crops on concentration (41% yield in all). The crude material obtained on evaporation of the mother liquors could not be separated into its components on a column of silica gel.

Hexahydrocolchiceine had a specific rotation $[\alpha]^{17°C}_{5461} = -232.$ for a 1% solution in chloroform. (Found: C,60.74; H,7.59; N,3.70%. After drying at 100° under reduced pressure, found: C,60.71; H,7.51; Calc. for $C_{21}H_{29}O_6N$: C,64.5; H,7.4; N,3.6. Calc for $C_{20}H_{29}O_7N$: C,60.8; H,7.3; N,3.5).

The diacetate was obtained on treating the diol (0.1g) with acetic anhydride (0.2cc) in pyridine (3cc), and furnished colourless needles from ethyl acetate, m.p.166°.

Attempted reduction of Colchiceine

(i) By Hydrogenation over Palladium.

Colchiceine (0.3g) in acetic acid (5cc) slowly absorbed hydrogen in the presence of palladium black (0.1g) at room temperature, the absorption (2.7 moles) being complete after fifteen hours. The evaporated filtrates were separated into acidic and neutral fractions by extraction with chloroform and caustic soda solution. The acidic material was recovered colchiceine (0.03g). The neutral gum did not crystallise, even on seeding with hexahydrocolchiceine.

(ii) With Zinc and Acetic Acid

Colchiceine (0.5g) was refluxed for six hours with zinc dust (1g) in aqueous acetic acid (75%, 10cc). The filtered and concentrated solution was separated into neutral and acidic fractions. The neutral gum (0.25g) could not be induced to crystallise. The acidic fraction was recovered colchiceine (0.2g).

(iii) With Raney-nickel alloy

Colchiceine (0.5g) in solution in hot (90°) caustic soda solution (30cc of 10%) was treated with Raney-nickel alloy in small amounts aver half-an-hour, while stirring vigorously. After an hour at 90°, the cooled suspension

was extracted with butanol which was filtered, dried, and concentrated. The residual neutral gum (0.44g) was not obtained in a crystalline state.

Attempted Hydrogenation of Hexahydrocolchiceine

Pure hexahydrocolchiceine showed no evidence of absorption of hydrogen even with very active platinic oxide catalyst, and in the presence of ferrous salts as promoters.

One sample of the diol (m.p. and mixed m.p. 202°-203°) on microhydrogenation over platinic oxide absorbed hydrogen (equivalent to 0.9 double-bonds) on two occasions. The evaporated filtrate, however, furnished unchanged starting-material (from aqueous methanol) m.p. 190° raised to 195° on admixture with the diol.

Tests with Osmic Acid Reagents

(i) Potassium Triacetyl Osmiate was obtained in solution by dissolving potassium methyl osmiate (compare Criegee[41]) in acetic acid. The colour of the solution is royal blue.

Substance	Colour Change in Potassium Triacetyl Osmiate
Hexahydrocolchiceine	Immediate change to yellow-brown
Diacetate of above	no reaction
Colchicine	no reaction
Colchiceine	Immediate change through yellow to orange
Salicylaldehyde	no reaction
Benzoin	no reaction

(ii) Osmium Trioxide Reagent

The crystalline reagent (0.1g, see Criegee[41]) in methanol was added to hexahydrocolchiceine (0.1g) in methanol, and the solution left overnight at room temperature. The residue, left after evaporation, could not be induced to crystallise and it slowly deposited a black precipitate of osmium on standing. The gum appeared to be a true complex, since, on shaking the chloroform solution with aqueous alkaline mannitol, the osmic acid complex of mannitol was formed very slowly during two hours and the diol was thereafter recovered in reduced amount (70%, m.p. and mixed m.p. 200°-201°) In contrast to this behaviour, free osmium trioxide reagent is instantaneously removed from a chloroform solution when it is shaken with alkaline mannitol solution.

Oxidations of Hexahydrocolchiceine

(i) With Chromic Acid

Hexahydrocolchiceine (0.1g) in glacial acetic acid (1cc) was treated dropwise, at room temperature, with a solution of chromic anhydride (0.04g) in acetic acid (1cc), the addition taking two hours. After a further hour, the diluted solution was extracted with chloroform which was washed with caustic soda, dried, and evaporated. The neutral fraction did not give a precipitate with 2:4-dinitrophenylhydrazine, and could not be induced to crystallise. The acidic fraction (obtained on acidification of the alkaline washings) was an intractable gum.

(ii) With Potassium Permanganate

Hexahydrocolchiceine (0.1g) in solution in pure acetone (3cc) was treated with a 3% solution of potassium permanganate in pure acetone (3cc) and left for 24 hours at room temperature, the solution being kept acid by the addition of small quantities of acetic acid from time to time (0.02g in all). The filtered solution was evaporated to dryness and separated into neutral and acidic fractions. The neutral material was unchanged diol (0.08g, m.p. and mixed m.p. 180°-190°). The acidic material could not be induced to crystallise.

Treatment of Hexahydrocolchiceine with Phosphorus Pentoxide.

The hexahydride (0.1g) was suspended in hot dry xylene (40cc) with phosphorus pentoxide (1g) for half-an-hour. The hot solution was decanted through a filter, and the evaporated filtrate was subjected to distillation under reduced pressure. A mobile oil distilled at 100°/10mm followed by a viscous gum (bath temp.130°/1.5mm) which did not crystallise. The lower-boiling fraction was later shown to be an impurity in the xylene. (Found: C,90.1; H,10.3%) . The phosphorus pentoxide residues yielded no basic material when dissolved in water and then made alkaline.

Attempt to Oximate Colchiceine in Strong Alkali

Colchiceine (0.14g) was recovered unchanged after one hour's heating at 100° with hydroxylamine hydrochloride (0.07g) in caustic potash solution (.8cc of 2N solution). M.p. and mixed m.p. 140°-150° after crystallisation from aqueous methanol.

1-Amino-1:3-diphenylpropane (LXXV)

Dihydrochalkone (5g) was heated for six hours at 175°-185° with formamide (5g). The resultant solution was diluted with water and extracted with ether which was dried and concentrated. The crude product was then boiled for one hour with concentrated hydrochloric acid (60cc) and water (40cc). On cooling the hydrochloride separated (68% yield) and was washed with ether to remove unchanged ketone. The hydrochloride gave colourless needles m.p. 190°-194° (from dilute hydrochloric acid). The picrate gave lemon-yellow plates (from aqueous ethanol) m.p. 183°-185° (Found: C,57.5; H,4.3; $C_{21}H_{19}O_7N_4$ requires C, 57.4; H,4.3%). Henrich[54] gives m.p. 195° for the hydrochloride, m.p. 155° for the picrate.

The amine was acetylated by shaking the hydrochloride with acetic anhydride and cuastic soda solution. The mixture was extracted with ether, which was then washed with acid, dried, and concentrated. 1-Acetylamino-1:3--diphenylpropane, gave colourless needles m.p.76°-77° (from benzene/petroleium) (Found: C,80.8; H, 7.5 ; $C_{17}H_{19}ON$ requires; C,80.7; H,7.5%).

Deamination of 1-Acetylamino-1:3-diphenylpropane

The acetyl derivative (0.5g) was refluxed for half-an-hour in pure dry xylene (20cc) with phosphorus pentoxide (2g), which rapidly darkened in colour. The combined xylene filtrate and washings were concentrated, when the residue distilled as a colourless oil at 140°-160° (bath temp.)/1mm. Yield 87%. Bromination in carbon disulphide gave colourless needles of 1:3-diphenylpropylene dibromide[55] (from ethanol) m.p. and mixed m.p. 108°-110°.

Attempted Deamination of 2-Amino--1:3-diphenylpropane (LXXIV)

The corresponding hydrochloride (300 mg) was converted to the free base by shaking with dilute caustic soda and ether. The evaporated extract was dried at 100° in vacuo, and the dry amine was thereafter refluxed in pure dry xylene (10cc) with phosphorus pentoxide (2g) for half-an-hour. The decanted concentrated xylene solution yielded only a trace of basic, saturated material. The phosphoric oxide, still pure white, yielded the unchanged base (87% recovered) after dissolving in water and making alkaline - m.p. of hydrochloride and mixed m.p. with starting material 198° -200°.

Attempted Identification of Cyclohexene

To obtain cyclohexene dibromide in a pure stable condition, the conditions of bromination advocated in Ref. 56 must be rigidly adhered to.

Cyclohexene dibromide was refluxed for one hour with p-thiocresol (2 moles) and aqueous caustic soda (2 mols) in sufficient ethanol for homogeneous solution. On dilution and cooling di-p-tolyldisulphide was obtained, m.p. 46° -47° (after crystallisation from ethanol). Similarly the dibromide gave no derivative with 2:5-dichlorophenylthiol[57] (i) in alcoholic solution in presence of an equivalent amount of caustic soda, when di-(2:5-dichlorophenyl)-disulphide (m.p. and mixed m.p. 80°) was the only solid product, or (ii) in xylene over excess potassium carbonate.

Heating of cyclohexenedibromide with o-phenylene diamine caused evolution of free bromine, and no solid derivative was obtained.

Deamination of N-Acetylcyclohexylamine

Acetyl cyclohexylamine (12g) in pure dry xylene (35cc) over phosphorus pentoxide (10g) was heated in a

distillation flask. At 90° the pentoxide darkened in colour and a low-boiling liquid was set free. By keeping the bath at 135° this liquid was caused to distil slowly over one hour, The temperature was now raised and half the xylene was allowed to distil.

The low-boiling distillate was separated into a water-soluble and an insoluble fraction by washing with water (three lots of 3cc). The soluble material, "salted out" by saturating the solution with potassium carbonate, was a colourless oil (b.p. 79° at 755mm). This oil was acetonitrile, since, on reduction (with sodium in ethanol), it yielded ethylamine, identified by formation of the picrate (m.p. and mixed m.p. 168°-170°), and by reaction with 2:4-dinitrochlorobenzene to give 2:4-dinitrophenylethyl-amine (m.p. and mixed m.p.113° -114°). The yield of acetonitrile was 39%.

The insoluble portion of the low-boiling distillate, distilled at 81°/760mm as a colourless mobile oil (19% yield) with a characteristic smell of cyclohexene. A portion of this oil (0.5g) was oxidised with excess potassium permanganate solution (50cc of 5% solution). After reduction of the excess permanganate (with sulphurous acid), the filtered alkaline solution was

evaporated to small bulk, and acidified, while hot, with concentrated hydrochloric acid. The fine crystals of inorganic salts (obtained by rapid chilling) were filtered off, dried thoroughly, and extracted with dry ether in a Soxhlet extractor. Adipic acid (m.p. and mixed m.p. 151° -152°) separated from the ether.

The xylene distillate was titrated at -5° with standard bromine (in carbon tetrachloride). The dibromide, after removal of xylene (by distillation under reduced pressure), was washed with ethanolic caustic potash, and then distilled as a colourless oil b.p. 88°/10 mm having the smell of cyclohexene dibromide. The uptake of bromine during titration was equivalent to a further yield of 17% of cyclohexene. The total yield of the latter is accordingly 36%.

Attempted Deamination of N-Acetylethylamine

Acetylethylamine (b.p. 206° -208°/755mm, 0.5g) dissolved in pure dry xylene (5cc) was heated with phosphorus pentoxide. A slow stream of dry nitrogen was bubbled in, and the emergent gases were bubbled through a dilute solution of bromine in ethanol. The pentoxide rapidly darkened in colour at 110° (bath temp.)

but no gases were evolved and the bromine was not decolorised. The alcoholic solution in the bubbler was freed from bromine with alcoholic caustic potash and then refluxed with potassium 2:5-dichlorothiophenate. Di-(2:5-dichlorophenyl)-disulphide was the only solid product. The phosphorus pentoxide residues when dissolved in water and then made alkaline, furnished a little free ethylamine (6% recovered) (identified by formation of 2:4-dinitrophenylethylamine m.p. and mixed m.p. 112° -114°).

Under exactly similar conditions, but replacing acetylethylamine with ethanol, the ethylene, formed by dehydration of the ethanol, was readily detected. The bromine solution in the bubbler was rapidly decolorised, and furnished ethylene bis-(2:5-dichlorophenyl)-disulphide (58) m.p.125°, after refluxing with 2:5-dichlorophenylthiol.

N-Acetyl-n-propylamine

Propionitrile (6g) was reduced with sodium (4.5g) in ethanol (60cc). The solution was then made acid with concentrated hydrochloric acid, evaporated to small bulk, made alkaline, and the propylamine distilled as

a strong aqueous solution, (picrate m.p.135°). The cooled, (0°) solution was acetylated with acetic anhydride, and the acetyl derivative, "salted out" with sodium hydroxide, distilled at 216°/755mm.

The acetyl derivative was refluxed with phosphorus pentoxide in xylene. The resultant gases (washed with nitrogen) did not decolorise a very dilute solution of bromine in carbon tetrachloride, and propylene dibromide could not be detected in the solution afterwards.

Identification of Propylene

Propylene is readily converted to the dibromide, on bubbling into a solution of bromine in ether.

The dibromide (1g) was refluxed in ethanol for four hours with 2:5-dichlorophenylthiol (1.8g) neutralised with alcoholic potassium hydroxide. The concentrated solution was diluted with water, and extracted with ether, which was washed with dilute caustic soda, dried, and evaporated. The residue, which could not be brought to crystallise, was oxidised at 100° with hydrogen peroxide (4cc of "100 volume" solution) in glacial acetic acid (20cc). After evaporation to dryness, the residue gave colourless needles of propylene bis-(2:5-dichloro-

-phenylsulphone) m.p.144° -145° (Found: C,39.7; H,2.7; $C_{15}H_9O_4Cl_4S_2$ requires C,39.0; H,2.7)

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